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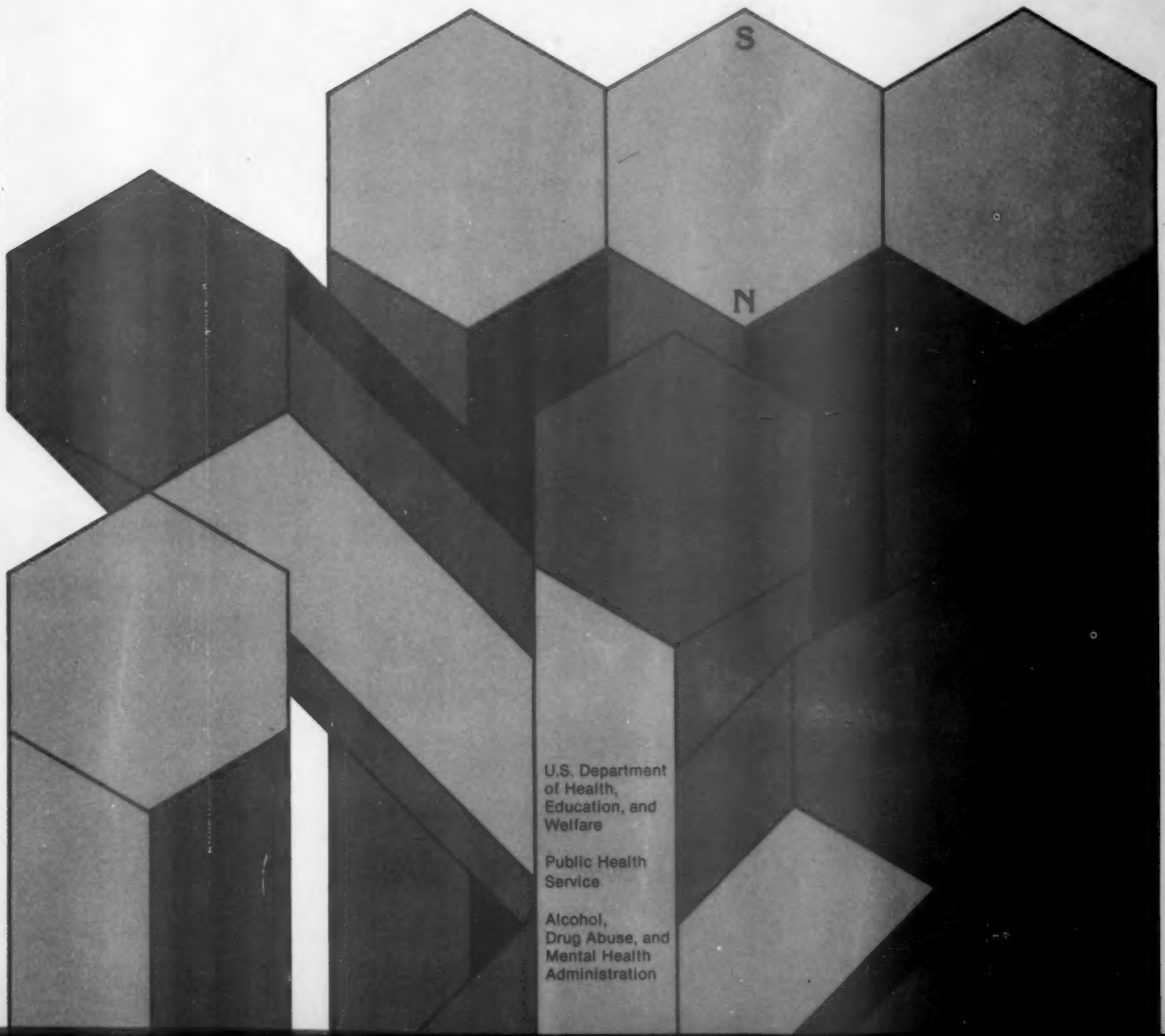

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Volume 16, Number 3 January 1979

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ABSTRACTS

PRECLINICAL PSYCOPHARMACOLOGY

01 CHEMICAL SYNTHESIS, ISOLATION AND CHARACTERIZATION

001942 Boswell, Robert F., Jr.; Welstead, William J., Jr.; Duncan, Robert L., Jr.; Johnson, David N.; Funderburk, William H. A. H. Robins Company, Richmond, VA 23220 **(1-(3-Phenothiazin-10-yl)propyl)-4-piperidinyl) phenylmethanones, a novel class of long-acting neuroleptic agents.** Journal of Medicinal Chemistry. 21(1):136-139, 1978.

A short series of (1-(3-(phenothiazin-10-yl)propyl) 4-piperidinyl) phenylmethanones was prepared and tested for neuroleptic activity using the blockade of d-amphetamine lethality in aggregated mice and suppression of conditioned avoidance behavior as the end points. Most compounds were shown to be potent neuroleptic agents and two were found to possess a long duration of action. 6 references. (Author abstract modified)

001943 Carnmalm, B.; Ramsby, S.; Renyi, A. L.; Ross, S. B.; Ogren, S.-O.; Stjernstrom, Nils E. Department of Organic Chemistry, Research and Development Laboratories, Astra Lakemedel AB, S-15185 Sodertalje, Sweden **Antidepressant agents. 9.3,3-Diphenylcyclobutylamines, a new class of central stimulants.** Journal of Medicinal Chemistry. 21(1):78-82, 1978.

3,3-Diphenylcyclobutylamine, N-methyl-3,3-diphenylcyclobutylamine, and N,N-dimethyl-3,3-diphenylcyclobutylamine have been prepared and tested in mice as potential antidepressant agents. The secondary and tertiary amines strongly decrease the accumulation of noradrenaline (NA) and serotonin (5-HT) in brain slices in vitro and in vivo. The cyclobutylamines also cause motor stimulation. The most potent compound in this respect is the tertiary amine 7. The increase in locomotion is not blocked by pretreatment with phenoxybenzamine, methergoline, or alpha-methyltyrosine. Pretreatment with pimozide or reserpine reduces the hyperactivity induced by 7. This hyperstimulation seems to be caused by a mechanism of action which differs from that of amphetamine. It is concluded that tertiary amine 7 may cause increase in locomotion by release of dopamine from granular stores. 25 references. (Author abstract)

001944 Ellis, K. O.; White, R. L.; Schwan, T. J.; Wessels, F. L. Division of Biological Research, Norwich-Eaton Pharmaceuticals, Morton-Norwich Products Incorporated, Norwich, NY 13815 **Synthesis and comparative skeletal muscle relaxant activity of some 2,4-imidazolidinediones and their corresponding 5-hydroxy-2,4-imidazolidinediones.** Journal of Medicinal Chemistry. 21(1):127-130, 1978.

A series of 5-hydroxy substitution products of 2,4-imidazolidinediones, including the 5-hydroxy metabolite of the skeletal muscle contraction antagonist, dantrolene sodium, has been synthesized and evaluated for skeletal muscle relaxant activity. Most of these analogues are active in vivo with intravenous administration and in vitro. While two analogues are also active by oral and intraperitoneal administration, only 1-(((5-(3,4-dichlorophenyl)-2-furanyl)methylene)amino)-5-hydroxy-2,4-i idazolidinedione is sufficiently active in inhibiting the Straub tail in mice. However, none of these analogues has a muscle relaxant efficacy, comparable to dantrolene. 18 references. (Author abstract)

001945 Florvall, Lennart; Ask, Anna-Lena; Ogren, Sven-Ove; Ross, Svante B. Department of Pharmacology, Research and Development Laboratories, Astra Lakemedel AB, S-15185 Sodertalje, Sweden **Selective monoamine oxidase inhibitors. 1. Compounds related to 4-aminophenethylamine.** Journal of Medicinal Chemistry. 21(1):56-63, 1978.

A series of derivatives of 4-aminophenethylamine was synthesized and their effect on monoamine oxidase (MAO) activity in mouse brain was evaluated. Several of the new compounds were potent and selective inhibitors of the A form of MAO but were poor inhibitors of the B form. The most active compounds were the 2,6-dichloro and the 2-halogeno-4-dimethylaminophenethylamines. Some of the compounds also strongly antagonized aggressive behavior in isolated male mice. This effect was correlated to the MAO inhibition when tyramine was used as substrate. Significant correlations between MAO inhibition in vivo and potentiation of the syndromes produced by 5-hydroxytryptophan and tryptamine and antagonism of reserpine sedation were obtained. 25 references. (Author abstract)

001946 Loew, Gilda H.; Berkowitz, Donald S. Department of Genetics, Stanford University Medical Center, Stanford, CA 94305 **Quantum chemical studies of N-substituent variation in the oxymorphone series of opiate narcotics.** Journal of Medicinal Chemistry. 21(1):101-106, 1978.

Quantum chemical calculations were performed on six N-derivatives of oxymorphone including N-methyl- (oxymorphone), N-allyl- (naloxone), N-dimethylallyl- (nalmexone), N-methylcyclopropyl- (naltrexone), N-methylcyclobutyl- (nalbuphone), and N-phenethylnoroxymorphone to identify conformational features of the N-substituents which might be responsible for the intrinsic observed pharmacological properties of opiate agonism and antagonism. Both axial and equatorial N-substituent conformers were considered, as well as possible interactions of the C14-OH group with such substituents. Variations of agonist/antagonist potency ratios within this series could not be explained by differing relative energies of equatorial and axial conformations or by varying rates of interconversion between the two. Direct effects of the C14-OH group on conformations of N-substituents also could not account for their relative agonist/antagonist potencies. Consistent with a previous hypothesis, the observed potencies and binding data could be explained most consistently by the availability of several low-energy equatorial conformations of N-substituents and their interactions with the C14-OH group through a common anionic receptor site. 29 references. (Author abstract)

001947 Miller, Richard J.; Chang, Kwen-Jen; Leighton, Jeff; Cuatrecasas, Pedro. Dept. of Pharmacological & Physiological Sciences, University of Chicago, 947 East 58th St., Chicago, IL 60637 **Interaction of iodinated enkephalin analogues with opiate receptors.** Life Sciences (Oxford). 22(5):379-388, 1978.

The synthesis and biological activity of radioiodinated derivatives of the metabolically stable enkephalin analogs, (DAla2,Leu5) and (DAla2,DLeu5)-enkephalin, are described. These derivatives show sterospecific binding to receptors in brain and homogenates and some neuroblastoma cell lines such as NG108-15 and N4TG1. The relative effects of levorphanol and dextrorphan and Naplus and Mnplus2 ions on enkephalin binding in brain and cells indicate that the

iodinated derivatives interact with opiate receptors. Levorphanol is considerably more potent in displacing specifically bound enkephalin than dextrorphan. Sodium ions at physiological concentrations decrease enkephalin binding whereas manganese ions enhance it. Unlabeled monoiodo derivatives retain high potency in the guinea-pig ileum, mouse vas defernes and receptor binding assays. Unlabeled diiodo derivatives show far lower potency in these assays. It is concluded that radioiodinated derivatives containing one iodine per molecule retain high affinity for the opiate receptor but diiodo derivatives do not. 18 references. (Author abstract modified)

001948 Pelletier, Georges; Dube, Donald; Puviani, Romano. Medical Research Council Group in Molecular Endocrinology, CHUL, Quebec GIV 4G2, Canada **Somatostatin: electron microscope immunohistochemical localization in secretory neurons of rat hypothalamus.** Science. 196(4297):1469-1470, 1977.

Localization of somatostatin in secretory neurons of rat hypothalamus by using electron microscope immunohistochemistry was discussed. The brains of seven adult rats were fixed by perfusion with paraformaldehyde or glutaraldehyde in sodium cacodylate buffer. The hypothalami were dissected immediately after the perfusion and embedded in araldite. The somatostatin was stained using the peroxidase antiperoxidase technique. Somatostatin was observed in the secretory granules of a few neurons located in the hypothalamic periventricular nucleus. The results suggest that neurosecretory neurons are involved in the regulation of adrenohypophyseal secretion. 8 references. (Author abstract modified)

001949 Remy, David C.; Rittle, Kenneth E.; Hunt, Cecilia A.; Anderson, Paul S.; Arison, Byron H.; Merck Sharp & Dohme Research Laboratories, West Point, PA 19486 **Synthesis and stereospecific antipsychotic activity of (-)-1-cyclopropyl methyl-4 (3-trifluoromethylthio 5H-dibenzo(a,d)cycloheptene) piridine.** Journal of Medicinal Chemistry. 20(8):1013-1019, 1977.

The synthesis and resolution of 3-iodocyproheptadine ((plus or minus)-5a) and 1-cyclopropylmethyl-4 (3-iodo-5H-dibenzo(a,d)cyclohepten-5-ylidene) piperidine ((plus or minus)-5b) are described. The resulting atropisomers undergo reaction with trifluoromethylthiocopper to give optically active products without extensive racemization. In this manner, optically pure (+)- and (-)-3-trifluoromethylthiocyproheptadine ((+)-6a and (-)-6a, respectively) and (+)- and (-)-1-cyclopropylmethyl-4 (3-trifluoromethylthio-5H-dibenzo(a,d) cyclohepten-5-ylidene)piperidine ((+)-6b and (-)-6b, respectively) have been prepared. The influence of a chiral europium shift reagent on the proton and fluorine resonance signals as a diagnostic tool for the determination of the optical purities of these atropisomers is discussed. The four compounds, (+)-6a, (-)-6a, (+)-6b, and (-)-6b, were studied in squirrel monkeys for the ability to block conditioned avoidance responding. All of the antiavoidance activity was found to reside solely in the levorotatory compounds (-)-6a and (-)-6b. Further comparison of the enantiomers (-)-6b and (+)-6b showed that the ability to antagonize apomorphine-induced stereotyped behavior is confined to the levorotatory isomer (-)-6b while weak central anticholinergic activity resides solely in the dextrorotatory isomer (+)-6b. Neither (-)-6b nor (+)-6b has significant peripheral anticholinergic activity. 16 references. (Author abstract)

001950 Sapper, Helmut; Lohmann, Wolfgang. Institut fur Biophysik der Universitat, D-63 Giessen, Germany **Association of some psychotomimetic compounds with 6-methylpurine in aqueous solutions.** Biochemical Pharmacology (Oxford). 27(4):595-599, 1978.

The interaction between serotonin (5-HT) or stereochemically similar psychotomimetic drugs (mescaline, N,N-dimethyltryptamine, and D-lysergic acid diethylamide) and 6-methylpurine in aqueous solutions was investigated by means of nuclear magnetic resonance and osmometric techniques. The complex chemical shifts and the thermodynamic quantities of the association were evaluated. Relevant association models are discussed. Contrary to their mode of self-association the various drugs seem to interact with 6-methylpurine due mainly to their aromatic ring systems. In this way they might simulate the action of D-lysergic acid diethylamide. 14 references. (Author abstract modified)

001951 Strauss, Michael J.; Bard, Raymond R.; Robinson, Donald S. Department of Chemistry, College of Medicine, University of Vermont, Burlington, VT 05401 **3-Benzazocine amidinium nitronates. An unusual type of opiate antagonist.** Journal of Medicinal Chemistry. 21(1):139-140, 1978.

An interesting type of 3-benzazocine ring system which contains amidine functionality has been found to have significant narcotic antagonist activity in mice. The isomeric 2-benzazocine, which incorporates similar structural features, except for the position of the ring nitrogen and adjacent phenyl substituent, is inactive. These 2- and 3-benzazocines can be synthesized in a single step from appropriately structured amidines and naphthalenes, and such syntheses may provide useful routes to new and interesting types of narcotic antagonists. 8 references. (Author abstract)

02 DRUG DEVELOPMENT (PRECLINICAL SCREENING)

001952 Borison, R.; Diamond, B.; Havdala, H. Department of Anesthesiology, Mount Sinai Hospital, Chicago, IL 60608 **A new neuromodulator of the extrapyramidal system (EPS).** Federation Proceedings. 36(3):394, 1977.

A neurotransmitter role for 2-phenylethylamine, an endogenous amphetamine-like compound, was proposed at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Rats pretreated with reserpine assumed a parkinsonian-like state which was reversed by d-amphetamine or phenylethylamine. When reserpine was combined with alpha-methyldopa hydrazine, a selective phenylethylamine depleter, the onset of d-amphetamine reversal was delayed, whereas the time for phenylethylamine reversal was shortened. Treatment of reserpinized rats with alpha-methyl-p-tyrosine, a catecholamine depleter which also slows brain phenylethylamine turnover, markedly delayed amphetamine time for reversal and completely blocked amphetamine-induced stereotypy, whereas latency to phenylethylamine reversal was shortened and phenylethylamine-induced stereotypy was only mildly antagonized. The fact that phenylethylamine reverses reserpine-induced behavior in the absence of catecholamines and is concentrated in the limbic system and corpus striatum indicates a significant role for it in the regulation of the extrapyramidal system as well as affective states. 4 references. (Journal abstract modified)

001953 Cohn, Marthe; Kraynack, Barry J.; Ganley, Charles J. Department of Anesthesiology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213 **Central nervous system effects of peptides found in brain and intestines.** Federation Proceedings. 36(3):395, 1977.

The effects of substance-P, glucagon, and secretin on behavior in the rat were discussed at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Substance-P and secretin induced barrel rotations, while glucagon produced, alternatively, barrel rotations and tight head to tail rotations. In rats pretreated with apomorphine, substance-P, glucagon, and secretin produced tight heat to tail rotations. The same three substances also produced hyperactivity and convulsions. It is suggested that substance-P, glucagon, and secretin, as well as thyrotropic releasing hormone, LH releasing hormone, and somatostatin, are either neurotransmitters or modulators of neurotransmission. (Journal abstract modified)

001954 Cools, Alexander R.; Gieles, Lucie C. M.; Janssen, Hendrik-Jan; Megens, Anton A. P. H. Dept. of Pharmacology, University of Nijmegen, Geert Grooteplein N 21, Nijmegen, The Netherlands **Morphine and its biphasic influence upon pharmacologically distinct dopaminergic systems within the feline caudate nucleus: a behavioural study.** European Journal of Pharmacology (Amsterdam). 48(1):67-85, 1978.

Behavioral changes subsequent to alterations in dopamine (DA) activity in caudate nucleus were studied in freely moving cats pretreated with a systemic injection of morphine (5mg/kg i.p.). Intracerebral, bilateral injections of dopamine and haloperidol into the rostromedial part of the caudate nucleus, respectively increased and decreased DA activity in this area; similar injections of (3,4-dihydroxyphenylamino)-2-imidazoline (DPI) and ergometrine into the anterodorsal part of the nucleus respectively increased and decreased DA activity within this region. Emphasis is placed on the effects of intracerebrally injected drugs on the morphine-induced, successively appearing depression, reorganization and ritualization. Administration of DA into the rostromedial part and of ergometrine into the anterodorsal part mainly potentiated depression and reorganization, and inhibited ritualization; haloperidol in the rostromedial part and DPI in the anterodorsal part inhibited depression and reorganization and potentiated ritualization. The hypothesis is advanced that an acute injection of morphine (5mg) affects different dopamine systems in a differential way: it is suggested that morphine inter alia produces a time dependent, biphasic shift in the normally occurring balance between rostromedial DA activity X and anterdorsal DA activity from an initial rostromedial DA activity during depression and reorganization to anterodorsal DA activity during ritualization. 49 references. (Author abstract modified)

001955 Ferraro, Douglas Peter. University of New Mexico, Albuquerque, NM 87106 **/Effects of cannabinoids on unlearned behavior in animals./** Preclinical effects: unlearned behavior. In: Petersen, R. C., Marihuana Research Findings: 1976. Rockville, MD, NIDA, Research Monograph No. 14, 1977. 251 p. (p. 86-102).

Relevant literature on the effects of unlearned behavior in different animal species produced by cannabinoids is reviewed. The majority of cannabinoid research on unlearned behavior has used delta9-tetrahydrocannabinol and delta8-tetrahydrocannabinol since these particular cannabinoids have been established as the major active components of marihuana samples. A second major reason for the renewed interest in the effects of cannabinoids on unlearned behavior is the recent derivation of potentially psychoactive drugs from cannabinoids and the need for a preclinical test to determine the activity of these derivatives. The four categories of unlearned behavior which are discussed in relation to cannabinoid effects are: gross behavior; spontaneous motor activity and exploration; consummatory behavior; and aggressive behavior. 101 references.

001956 Fregnan, G. B.; Vidali, M. Division Richerche Lusofarmaco, Milano, Italy **Pharmacological profile of a new psychotherapeutic agent: 4-p-fluorophenyl 5-N(N'-o-methoxyphenyl) piperazinoethyl 4-oxazolin-2-one (LR 511).** Pharmacology (Basel). 15(6):485-502, 1977.

A profile of the pharmacology and action of a new psychotropic agent, 4-p-fluorophenyl 5-N(N'-o-methoxyphenyl) piperazinoethyl 4-oxazolin-2-one (LR-511) is presented. LR-511 was able to modify the spontaneous or the specialized behavior of animals and to antagonize some CNS effects evoked pharmacologically, thus sharing a number of properties with neuroleptics and thymoleptics but revealing also evident differences. At low doses (1 to 10mg/kg p.o.)LR-511 greatly reduced the spontaneous and the amphetamine-induced locomotor activity, showing peculiarly flat dose response curves. Within the same dose range, the compound was also able to reduce the aggressivity induced by isolation and the exploring activity in a new environment, to abolish the conditioned avoidance reflex and the conditioned food intake (deltaW test) to antagonize the stereotypy evoked by amphetamine, the emesis induced by apomorphine, and the death caused by catecholamines. At higher doses (10 to 30mg/kg p.o.)LR-511 inhibited apormorphine-induced gnawing, revealed antinociceptive activity, possessed tryptaminergic, histaminergic and serotonergic blocking properties (while lacking, even at much higher doses, central and peripheral anticholinergic and anticonvulsant properties). At very high doses (30 to 80mg/kg p.o.), the compound potentiated some hypnotic drugs (while being completely devoid of hypnotic properties itself), caused hypothermia and catalepsy. Inhibition of righting reflex and muscle relaxation were observed only with doses of LR-511 superior to 100mg/kg p.o. The activity on the cardiovascular system was weak and very inconstant. Acute toxicity studies have indicated that the drug was atoxic either in mice and rats up to the dose of 2000mg/kg p.o.,or in rabbits and dogs up to 1000mg/kg p.o. Owing to its low toxicity, and to its strong psychotropic activity at very low dose levels, the therapeutic margin of safety of LR-511 appeared unusually great. It is concluded that no definitive classification of LR-511 should be attempted until its clinical effectiveness is established, since the compound may turn out to be either CNS depressant or CNS antidepressant. 13 references. (Author abstract modified)

001957 Ginos, James Z.; Brown, Francis C.; Cotzias, George C. Department of Neurology, Cornell University Medical Center, New York, NY 10021 **Study of a dopaminergic potential antiparkinson compound in intact and nigra-lesioned rats: N-n-propyl-N-n-butyl beta-(3,4-dihydroxyphenyl) ethylamine HCl.** Federation Proceedings. 36(3):394, 1977.

Comparison of a new dopaminergic, antiparkinsonion drug, N-n-propyl-N-n-butyl beta-(3,4-dihydroxyphenyl) ethylamine HCl and apomorphine in intact and nigra lesioned rats was reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Both the ethylamine and apomorphine induced identical stereotypy in intact and lesioned rats, but the stereotypy in the intact rats differed from that in lesioned rats. In the lesioned rats, concentrations of the new compound in the blood correlated strikingly over a 1 hr period with rotations/min, but the correlation was lower in the intact animals. O-methylation of the ethylamine compound was quantitative and rapid in comparison with apomorphine, which may explain why higher

doses were necessary for comparable behavioral effects. Further study of this new compound and eventual clinical trials are recommended. (Journal abstract modified)

001958 Tornheim, Patricia A.; McLaurin, Robert L. Dept. of Anatomy, University of Cincinatti, College of Medicine, Cincinnatti, OH **Effect of dexamethasone on cerebral edema from cranial impact in the cat.** Journal of Neurosurgery. 48(2):220-227, 1978.

The effect of dexamethasone on cerebral edema from cranial impact, which in human subjects can lead to altered states of consciousness and coma, studied in an animal model of head trauma using cats. A Remington humane stunner was used to deliver blows to the skulls of anesthetized cats. Alternate animals were posttreated with either dexamethasone (4mg/kg/day) or a comparable volume of saline. Each animal was tested for cerebral edema 48 hrs after impact by measurement of the change in density of white matter from normal values. Dexamethasone therapy did not reduce the change in density of hemispheres with contusions involving both cortex and underlying white matter. For hemispheres with contusions limited to cerebral cortex, there was minimal edema of the white matter, which was reduced a slight amount by dexamethasone. It is suggested that the search for therapeutic measures for trauma-induced brain edema is necessary. 17 references. (Author abstract modified)

001959 VonVoigtlander, P. F.; Triezenberg, H. J.; Losey, E. G. Upjohn Company, Kalamazoo, MI 49001 **Interactions between clonidine and antidepressant drugs: a method for identifying antidepressant-like agents.** Federation Proceedings. 36(3):289, 1977.

Alteration of the hypothermic effect of clonidine by antidepressants in mice will be discussed at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Antidepressant drugs are known to antagonize the hypotensive effects of clonidine. Clonidine was found to lower body temperature in mice in a dose dependent manner. A single dose of antidepressant did not block this hypothermic effect, but multiple doses of antidepressants over 1 to 4 days caused increasing antagonism of the hypothermia. This property was shared by the classical tricyclic drugs as well as by iprindole, opipramol, trimipramine, nomifensine, viloxazine, and alpha-adrenergic blocking agents, but not by beta-adrenergic blocking agents, CNS stimulants, major tranquilizers, sedatives, or anticholinergic agents. The delayed effect of antidepressants in this test is reminiscent of the delayed onset of clinical activity of these drugs. (Journal abstract modified)

001960 Waldmeier, Peter C.; Baumann, Peter A.; Wilhelm, Max; Bernasconi, Raymond; Maitre, Laurent. Research Dept., Pharmaceuticals Division, Ciba-Geigy AG, Basle, Switzerland **Selective inhibition of noradrenaline and serotonin uptake by C 49802-B-Ba and CGP 6085 A.** European Journal of Pharmacology (Amsterdam). 46(4):387-391, 1977.

The effects of two new potential antidepressant compounds, 1-(1-methylamino-2-hydroxy-3-propyl) dibenzo(b,e)bicyclo(2,2,2)octadin HCl (C-49802-B-Ba) and 4-(5,6-dimethyl-2-benzofuranyl)piperidine HCl (CGP-6085-A), on serotonin and noradrenaline uptake were investigated in rats using different test systems. Results indicate that CGP-6085-A is a very potent and selective inhibitor of serotonin uptake in rat brain (ED50 1 to 4mg/kg p.o.,depending on test system); doses up to 1000mg/kg p.o. did not inhibit noradrenaline uptake. C-49802-B-Ba is a potent and selective inhibitor of noradrenaline uptake in rat brain (ED50 5 to 10mg/kg p.o.,depending on test system) and heart (ED50 1.5mg/kg p.o.). At 300mg/kg p.o.,this compound caused no inhibition of serotonin uptake. 12 references. (Author abstract modified)

03 MECHANISM OF ACTION: PHYSIOLOGICAL, BIOCHEMICAL AND PHARMACOLOGICAL

001961 Adcock, Tina; Taberner, P. V. Dept. of Pharmacology, University of Bristol, Bristol BS8 1TD, England **Measuring changes in cerebral glutamate and GABA metabolism prior to convulsions induced by 3-mercaptopropionate.** Biochemical Pharmacology (Oxford). 27(2):246-248, 1978.

Problems associated with measuring changes in cerebral glutamate and GABA metabolism prior to convulsion induced by 3-mercaptopropionate (MP) are reviewed, and a method which may eliminate most neurochemical assay problems is described. This method (which involves the calculation of theoretical enzyme inhibition) is only applicable to completely reversible inhibitors, since it is only then that the dilution of the inhibitor from its in vivo concentration results in an underestimate of the effective inhibition in vivo. Results indicate a very rapid onset of the biochemical effects of MP following its injection, which suggests that if MP is acting by interfering with the action of inhibitory GABA neurons, then newly synthesized GABA must be essential for maintaining an adequate supple of releasable GABA in the nerve terminal. 30 references.

001962 Argiolas, A.; Paglietti, E.; Fadda, F.; Quarantotti, B. Pellegrini; Gessa, G. L. Institute of Pharmacology, University of Cagliari, Cagliari, Italy **Effect of psychotropic drugs on 3,4-dihydroxyphenylacetic acid (DOPAC) content in the medial basal hypothalamus.** Life Sciences (Oxford). 22(6):461-466, 1978.

The effect of different psychotropic drugs on 3,4-dihydroxyphenylacetic acid (DOPAC) levels in the medial basal hypothalamus was studied, using a sensitive radioenzymatic method. Apomorphine and haloperidol, which are known to respectively decrease and increase DOPAC levels in the caudate nucleus, fail to influence DOPAC level in the medial basal hypothalamus. Reserpine, which increases DOPAC level in the caudate nucleus, decreases it in the medial basal hypothalamus. Amphetamine decreases DOPAC level in the medial basal hypothalamus as it does in the caudate nucleus. These results suggest that dopamine metabolism in the medial basal hypothalamus is controlled by mechanisms different from those operating in other brain areas. 15 references. (Author abstract)

001963 Austen, B. M.; Smyth, D. G.; Snell, C. R. National Institute for Medical Research, Ridgeway, Mill Hill, London NW7, England **Gamma endorphin, alpha endorphin and Met-ankephalin are formed extracellularly from lipotropin C fragment.** Nature (London). 269(5629):619-621, 1977.

The extracellular formation of gamma endorphin, alpha endorphin and met-enkephalin from lipotropin C fragment is reported. The C fragment, or beta-endorphin, has been shown to produce profound and long-lasting analgesia and to possess morphinomimetic properties. It was degraded by membrane bound enzymes from rat brain to form the three small opiate-like peptides, and results indicated that the extracellular metabolism of the C fragment takes place in a specific manner to form this series of peptides. This may mean that the shorter peptides that were isolated are degradation products of C fragment, rather than natural peptides. It is premature, however,

to make a definitive conclusion, since it has been reported that enkephalin is present in rat brain even after rapid killing by microwave irradiation. 18 references.

001964 Bacopoulos, N. G.; Bhatnagar, R. K.; Van Orden, L. S., III. Dept. of Pharmacology, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06510 **The effects of subhypnotic doses of ethanol on regional catecholamine turnover.** Journal of Pharmacology and Experimental Therapeutics. 204(1):1-10, 1978.

To investigate the effects of subhypnotic doses of ethanol on the regional turnover of norepinephrine and dopamine, a study was conducted. A subhypnotic dose of ethanol given intraperitoneally to rats significantly reduced the turnover of dopamine in the substantia nigra and caudate nucleus, increased dopamine turnover in the olfactory tubercle and had no effect on dopamine turnover in the nucleus accumbens, amygdala and hypothalamus. The same dose of ethanol decreased the probenecid-induced homovanillic acid accumulation in the caudate nucleus. The turnover of norepinephrine decreased in hypothalamus and increased in the pons medulla region. Norepinephrine turnover was unaffected in frontal cortex, parietal cortex, cerebellum, anygdala, hippocampus and locus coeruleus region. The distribution of ethanol was similar in cortex, caudate nucleus, hypothalamus and pons/medulla. It was concluded that catecholamine turnover in different brain regions seems to be differentially sensitive to the effects of ethanol, with most regions being unaffected by ethanol. 54 references. (Author abstract).

001965 Baumann, P. A.; Maitre, L. Research Dept., Pharmaceuticals Division, Ciba-Geigy Ltd., CH-4002 Basle, Switzerland **Blockade of presynaptic alpha-receptors and of amine uptake in the rat brain by the antidepressant mianserine.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 300(1):31-37, 1977.

The effects of the antidepressant mianserine (Tolvon) on noradrenaline (NA) release and on amine uptake were investigated in rat cortical tissue slices previously labeled with 3H-NA. Mianserine increased the release of 3H-NA from field stimulated cortical slices. The drug failed to augment NA release further after blockade of the presynaptic alpha-adrenergic receptors by phentolamine. Phentolamine also failed to augment NA release after exposure of the tissue slices to mianserine. Mianserine also antagonized the reduction of NA release by clonidine in the same manner as did the alpha-blocking drugs phentolamine and phenoxybenzamine. In addition, mianserine inhibited NA uptake in vitro and in vivo (in the rat heart and midbrain/diencephalon synaptosomes from pretreated rats), but had only a marginal inhibitory effect on serotonin (5-hydroxytryptamine) uptake. It is concluded that the data support the hypothesis that the mianserine-induced release of NA is due primarily to the blockade of presynaptic noradrenergic alpha-receptors. It is proposed that mianserine increases the concentration of NA in the synaptic cleft by blocking the presynaptic alpha-receptors and by inhibiting amine uptake. 22 references. (Author abstract modified)

001966 Belcher, G.; Ryall, R. W. Department of Pharmacology, University of Cambridge, Cambridge CB2 2QD, England **Differential excitatory and inhibitory effects of opiates on non-nociceptive and nociceptive neurones in the spinal cord of the cat.** Brain Research (Amsterdam). 145(2):303-314, 1978.

To elucidate excitatory and inhibitory effects of opiates on nociceptive and nonnociceptive neurones in the spinal cord, morphine, levorphanol, dextrorphan and naloxone were applied microelectrophoretically to cells identified as either having nociceptive inputs or nonnociceptive inputs in the dorsal horn of the cat (n=37). Morphine excited nonnociceptive cells and depressed nociceptive cells. Naloxone reversed morphine excitations on nonnociceptive cells, but only reversed about one third of morphine depressions on nociceptive cells. Levorphanol depressed nociceptive cells, while dextrorphan ejected with similar currents caused less depression or had no effect. It is concluded that excitation of nonnociceptive cells may constitute a spinal action relevant to the analgesic action of opiates, acting synergistically with a depressant effect on nociceptive neurones. 48 references. (Author abstract modified)

001967 Bender, K. I.; Makarov, V. V. Kafera farmakologii, Saratovskiy meditsinskiy institut, Saratov, USSR **/Dependence of the influence of epinephrine on the excitability of giant neurons on its concentration./** Kontsentratsionnaya zavisimost' kharaktera vliyaniya adrenalina na vozbudimost' gigantskikh neyronov. Farmakologiya i Toksikologiya (Moskva). 40(2)148-153, 1977.

A study was made to determine whether the concentration of epinephrine affects its action on giant neuron excitability in the mollusc Limnaea stagnilis. Results showed a lesser concentration of epinephrine increased giant neuron excitability, while greater concentrations reduced excitability. Propranolol had no effect on epinephrine action in this regard, and dihydroergotoxin abolished the inhibitory effect of epinephrine. 13 references. (Journal abstract modified)

001968 Bhattacharya, S. K.; Sanyal, A. K. Dept. of Pharmacology, Institute of Medical Sciences, Banaras Hindu Univ., Varanasi 221005, India **Inhibition of pentylenetetrazol-induced convulsions in rats by prostaglandin E1: role of brain monoamines.** Psychopharmacology (Berlin). 56(2):235-237, 1978.

A study was conducted to determine the role of brain monoamines in the inhibition of pentylenetetrazol-induced convulsions in rats by prostaglandin E1. Prostaglandin E1 (PGE) induced inhibition of pentylenetetrazol (PTZ) convulsions in rats significantly antagonized after pretreatment with drugs known to reduce brain serotonin activity, but not by pharmacological agents that decrease brain catecholamine activity. PGF2alpha also significantly inhibited PGE1 action. The results suggest that PGE1 induced inhibition of PTZ convulsions is not a direct effect, but an indirect one mediated through increase in brain serotonin activity. 13 references. (Author abstract modified)

001969 Black, Michael Jeffery. Virginia Commonwealth University/Medical College of Virginia **Alteration of L-dopa effect on brain dopa and dopamine levels with nicotinic acid and N-methyl nicotinamide. (Ph.D. dissertation).** Dissertation Abstracts International. Ann Arbor, MI, Univ. M-films, No. 77-20969 HC$15.00 MF$8.50 169 p.

The alteration of the L-dopa effect on brain dopa and dopamine levels with nicotinic acid and N-methyl nicotinamide, proposed to decrease brain levels of S-adenosylmethionine (S-A), (a critical compound to catecholamine catabolism) was studied in rats. In preliminary studies to determine the effectiveness of a peripheral dopa decarboxylase inhibitor (N-seryl-N'-trihydroxybenzyl hydrazine) used with L-dopa treatment and the effectiveness of L-dopa treatment on elevation of brain dopa levels and on altering brain S-A levels, it was found that: 1) the peripheral dopa decarboxylase inhibitor was effective; 2) large brain dopa levels were found 2 hr.

after L-dopa treatment; and 3) in L-dopa treatment, brain S-A levels were lowered between 0.75 and 2.75 hrs. It was further found that oral L-dopa treatment most affected dopa and dopamine levels in brain, liver, and serum. Coadministration of L-dopa plus nicotinic acid or nicotinamide led to decreased brain dopa and dopamine levels compared to L-dopa alone, possibly because nicotinic acid may delay dopa and dopamine accumulation in the brain. At 3 hr. after administration, a delayed buildup of brain dopa and dopamine levels compared to L-dopa alone was observed with L-dopa plus nicotinic acid of N-methyl nicotinamide. It is concluded that altering the brain dopa and dopamine time course in L-dopa treatment with nicotinic acid or N-methyl nicotinamide may result in greater overall buildup of brain dopamine and thereby potentiate the action of L-dopa. This fact may prove helpful in Parkinson's disease therapy, but the mechanism of action is not known. (Journal abstract modified)

001970 Bobkiewicz, Teresa; Chodera, Alfons; Godlewski, Janusz; Nowakowska, Elzbieta. Zaklad Farmakologii i Farmakodynamiki Instytutu Biologiczno-Farmaceutycznego, Akademia Medyczna, 10 Fredry, Poznan 61-70, Poland **Effect of thymoanaleptic agents on the course of experimental arterial hypertension and catecholamine content in tissues and urine.** Acta Physiologica Polonica (Warszawa). 28(3):195-201, 1977.

The effect of thymoanaleptic agents on the course of experimental arterial hypertension and catecholamine content in tissues and urine, induced in rats by two methods is discussed. In the course of hypertension development the rats of experimental groups were treated with following tricyclic antidepressive agents: imipramine, opipramol, amitriptyline and nortriptyline injected in doses of 5.0or 0.5mg per 1kg of body weight. Higher doses of the above drugs inhibited the development of hypertension, whereas the lower doses had no effect on arterial blood pressure. 21 references. (Journal abstract modified)

001971 Boismare, F.; Le Poncin, M.; Lefrancois, J. Dept. of Pharmacology, Hotel-Dieu, rue de Lecat, F-76036 Rouen, France **Biochemical and behavioural effects of hypoxic hypoxia in rats: study of the protection afforded by ergot alkaloids.** Gerontology. 24(Supplement 1):6-13, 1978.

In a paper presented at a workshop on experimental pharmacology of hydergine in Basel, December 1976, research is reported in which the conditioned avoidance response and the cerebral levels of dopamine and nonadrenaline were studied in control rats and in rats submitted to a hypobaric hypoxia. A protection against the effects of hypoxia was induced by both dihydroergocornine and dihydroergocryptine and the noradrenaline level did not decrease. It was concluded that this stabilization of cerebral noradrenaline level was the main protection factor observed. 11 references. (Author abstract modified)

001972 Boisse, Norman R.; Okamoto, Michiko. Department of Medicinal Chemistry and Pharmacology, College of Pharmacy, Northeastern University, Boston, MA 02115 **Physical dependence to barbital compared to pentobarbital. II. Tolerance characteristics.** Journal of Pharmacology and Experimental Therapeutics. 204(3):507-513, 1978.

The tolerance characteristics of barbital are described as compared to pentobarbital, the standard drug, during chronically equivalent treatment. Barbiturate tolerance was assessed as the increase in dose from the beginning to the end of treatment required to achieve equieffective peak effect. Dispositional tolerance was assessed as a reduction in the elimination half-life of barbiturate from blood. Functional tolerance was assessed as the increase in blood concentration of barbiturate at the time of peak effect. Overall, greater tolerance was developed to pentobarbital than to barbital. For pentobarbital, tolerance was both dispositional and functional; the dispositional tolerance developed rapidly and was almost complete at 1 week. For barbital, tolerance was exclusively functional. Functional tolerance to barbital and pentobarbital developed at the same slow rate for chronically equivalent treatment. This finding suggests that functional tolerance development is independent of the particular barbiturate reflecting the adaptability of the central nervous system to chronic depression. 38 references. (Author abstract)

001973 Bondarenko, T. T. Lab. psikhofarm., Tsentral'nyy NII sudebnoy psikhiatrii im. V. P. Serbskogo, Ministerstvo zdravookhraneniya SSSR, Moscow, USSR /Neurochemical **mechanisms of central action of morphine on functions of single neurons in the midbrain reticular formation./** Izucheniye neyrokhimicheskikh mekhanizmov deystviya morfina na funktsii neyronov retikulyarnoy formatsii srednego mozga. Fiziologicheskiy Zhurnal SSSR imeni I. M. Sechenova (Leningrad). 63(6):782-788, 1977.

The effect of microiontophoretically applied morphine and its interactions with the effect of microiontophoretic applications of either acetylcholine or 5-hydroxytryptamine were studied in single neurons of the midbrain reticular formation in immobilized rats. Morphine altered the firing rate of the majority of neurons: 39% of the neurons were excited, and 16% were inhibited. Morphine reduced or blocked reactions of most (67%) neurons to 5-hydroxytryptamine but had no effect on their reactions to acetylcholine (86%). The findings suggest that interaction between morphine and serotoninergic structures of the brain has a more important role in the mechanism of morphine central action than the interaction between morphine and cholinergic systems. 20 references. (Journal abstract modified)

001974 Bouyer, Jean-Jacques; Dedet, Laure; Verdeaux, Jaqueline; Rougeul, Arlette. Lab. de Neurophysiologie comparee, Universite P. & M. Curie, 4 place Jussieu, F-75230 Paris Cedex 05, France **Selective modification of spontaneous ECoG rhythms of the cat somesthetic cortex by psychoactive drugs: behavioral correlates.** Psychopharmacology (Berlin). 55(3):237-242, 1977.

Three psychoactive drugs with known central effects, d-amphetamine, LSD-25, and Ditran, were administered to the freely moving cat to study their action on spontaneous rhythmic activities recorded from the primary somesthetic cortex, which are analogous to the rolandic mu rhythm in man. The ECoG patterns obtained are qualitatively identical to those of the normal subject, but their temporal organization is profoundly disturbed by the action of the drugs. The normal ECoG consists of three rhythmic systems with distinct frequencies and displays a considerable time variability. In contrast, psychoactive drugs induce a stablized pattern with only one type (or at most two types) of rhythm prevailing for 1 or several hours, which never occurs under normal conditions. These ECoG rhythms underlie various behavioral states. Under d-amphetamine, correspondence remains excellent between behavior and ECoG; under Ditran, complete dissociation occurs; finally, LSD represents a borderline case in which ECoG and behavior are partially correlated and partially dissociated. Results are also discussed as they relate to the different thalamocortical systems underlying ECoG rhythms. 26 references. (Author abstract modified)

001975 Bowers, C. Y.; Fong, B. T. W.; Chang, J. K. Tulane Medical School, New Orleans, LA 70112 **Pituitary hormone release in vitro by morphine-like-peptides.** Federation Proceedings. 36(3):311, 1977.

Structure/activity relationships between small peptides with opiate activity and pituitary hormone release in the rat were reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Studies were designed to determine whether these peptides or some of their derivatives or analogues stimulate release of LH, FSH, and/or TSH from the rat pituitary or inhibit the thyrotropin releasing hormone/TSH, LH releasing hormone/LH, or LH releasing hormone/FSH responses in vitro. The hormones beta-lipotropin (61-65), beta-endorphin, and gamma-endorphin did not possess any of the above properties at concentrations. Leu-enkephalin antagonized LH releasing hormone but not thyrotropin releasing hormone. Analogues with dopa, phenylalanine, tryptophan, or histidine in the 1 position of met-enkephalin antagonized LH releasing hormone. C-terminal amidated analogues of met-enkephalin and leu-enkephalin had agonist activity. LH and FSH were released by alpha-endorphin, but not by gamma-endorphin. (Journal abstract modified)

001976 Brown, Lucy L.; Wolfson, Leslie I. Saul R. Korey Dept. of Neurology, Albert Einstein College of Medicine, Bronx, NY 10461 **Apomorphine increases glucose utilization in the substantia nigra, subthalamic nucleus and corpus striatum of rat.** Brain Research (Amsterdam). 140(1):188-193, 1978.

Sokoloff's (1977) autoradiographic 2-deoxy-D-glucose (DG) technique was used to observe the action of apomorphine on substantia nigra and other extrapyramidal structures in awake freely moving rats. DG was used to monitor changes in grey matter metabolic activity; glucose utilization was also studied. Apomorphine increased glucose utilization in two extrapyramidal nuclei known to contain dopamine terminals and receptors: the substantia nigra and caudate nucleus. Significant increases in glucose utilization were also noted in the globus pallidus and subthalamic nucleus. Increases were relatively specific for dopamine agonists in that in all four regions the changes were blocked by pretreatment with haloperidol. Results are discussed in terms of effects of dopamine stimulation and the role of the various brain structures in dopaminergic control mechanisms. 19 references.

001977 Buice, R. G.; Bourn, W. M. School of Pharmacy, Northeast Louisiana University, Monroe, LA 71209 **Time course of audiogenic seizure susceptibility and plasma pentobarbital concentration during withdrawal.** Research Communications in Chemical Pathology and Pharmacology. 19(1):75-84, 1978.

In a study of the time course of audiogenic seizure susceptibility and plasma pentobarbital concentration during withdrawal, rats were made dependent on sodium barbital by daily oral administration of the drug over a 4 week period. At the end of this time the animals were switched to sodium pentobarbital every 4 hours for 3 days and withdrawn. Mean plasma pentobarbital concentration was observed to decline rapidly following peak concentrations which occurred approximately 1 hour after the final dose. The last samples in which pentobarbital was detectable were taken 3 hours after the last dose. Audiogenic seizure susceptibility and intensity peaked at 6 hours following the last dose, suggesting that a low concentration of barbiturate is more important in increasing seizure propensity than a sudden decrease in concentration. No electroencephalographic abnormalities were observed during the withdrawal period. 10 references. (Author abstract modified)

001978 Bulayev, V. M.; Ostrovskaya, R. U. Laboratoriya farmakologii nervony sistemy, Institut Farmakologii AMN SSSR, Moscow /**Effect of diazepam on pulse activity of neurons of the sensorimotor and optic areas of the rat cerebral cortex.**/ Vliyaniye diazepama na impul'snuyu aktivnost' neironov sensomotornoi i zritel'noi obltastei kory golovnogo mozga krys./ Byulleten' Eksperimental'noy Biologii i Meditsiny (Moskva). 83(2):183-185, 1977.

Threshold doses of diazepam influencing spontaneous and induced activity of neurons of the sensorimotor cortex in rats were determined. Acute experiments were performed on 54 unanesthetized, curarized rats, and recordings were made of the neuronal activity of the cortex. Diazepam proved to depress the spontaneous activity and induced activity of the sensorimotor neurons at considerably lesser doses than it did the neuronal activity of the optic cortex. It is supposed that neurons of the anterior portions of the cortex are more sensitive to diazepam than neurons of the limbic structures and the reticular formation. 13 references. (Journal abstract modified)

001979 Cahn, J.; Borzeix, M. G. Institute for Experimental Therapy and Clinical Research, F-92120 Montrouge, France **Comparative effects of dihydroergotoxine (DHET) on CBF and metabolism changes produced by experimental cerebral edema, hypoxia and hypertension.** Gerontology (Basel). 24(Supplement 1):34-42, 1978.

In a paper presented at a workshop on experimental pharmacology of hydergine in Basel, December 1976, a study on the comparative effects of dihydroergotoxine (DHET) on cerebral blood flow and metabolism changes produced by experimental cerebral edema, hypocia and hypertension in dogs, rabbits, and rats is reported. It was found that DHET perfused in the dog presenting cerebral perhypocapno anemic syndrome reduced cerebral hyperemia and favored glucose oxidation in the brain. Findings also indicated that DHET is able to drop mean, diastolic and systolic arterial blood pressures in renal hypertensive rats having a cerebral edema induced by triethyltin intoxication without affecting cerebral water and sodium levels which are increased in the controls. DHET can also improve EEG changes produced by a traumatic edema but does not exert any effect on EEG changes produced in the rabbit by lithium chloride intoxication. 10 references. (Author abstract modified)

001980 Calderini, Gabriella; Consolazione, Adriana; Garattini, Silvio; Algeri, Sergio. Istituto di Recherche Farmacologiche 'Mario Negri', Via Eritrea 62, I-20157 Milano, Italy **Different effects of methionine-enkephalin and (D-Ala2)methionine-enkephalin amide on the metabolism of dopamine and norepinephrine in rat brain: fact or artifact?** Brain Research (Amsterdam). 146(2):392-399, 1978.

In an attempt to extend previous findings of a similarity between morphine and enkephalin actions on catecholamines, changes in dopamine (DA) and norepinephrine (NE) were measured in rats following administration of methionine-enkephalin (met-enk) or (D-Ala2)methionine-enkephalin amide (D-Ala) into the lateral cerebral ventricles. Results indicate that met-enk decreases both DA and NE turnover, while D-Ala increases DA turnover but leaves NE turnover unchanged. The decrease in catecholamine turnover may however be a methodological artifact, and further research will be needed. D-Ala, on the basis of results, appears to be similar to morphine in its action on cortical DA. Unlike morphine, however, D-Ala appears to be inactive on cortical NE turnover. This may be due to the peptide's having difficulty in reaching the cortex, although effectiveness of action found in the limbic forebrain makes this explanation unlikely. 22 references.

001981 Carey, Robert J. Veterans Administration Hospital, Irving Avenue and University Place, Syracuse, NY 13210 **A comparison of food intake suppression produced by giving amphetamine as an aversion treatment versus as an anorexic treatment.** Psychopharmacology (Berlin). 56(1):45-48, 1978.

To examine the anorexic and aversive treatment effects of amphetamines on food intake, separate groups of rats were given either 1 or 2mg/kg injections of amphetamine 30 min before or after eating a preferred high fat food. When given before eating as an anorexic treatment, amphetamine initially suppresses intake almost completely, but with repeated injections tolerance developed. In contrast, amphetamine given after eating as an aversion treatment initially had little effect on intake, but with repeated injections it suppressed intake almost completely in rats receiving the higher dose. 15 references. (Author abstract modified)

001982 Caron, Marc G.; Raymond, Vincent; Lefkowitz, Robert J.; Labrie, Fernand. MRC Group in Molecular Endocrinology, CHUL, Quebec, PQ, Canada **Identification of dopaminergic receptors in anterior pituitary: correlation with the dopaminergic control of prolactin release.** Federation Proceedings. 36(3):278, 1977.

A study of the binding of tritiated dihydroergocryptine, a dopamine agonist, in bovine anterior pituitary membranes will be presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Binding was rapid, saturable, and reversible. Specificity of the interaction of dihydroergocryptine was typically dopaminergic, with stereoisomers of butaclamol, flupenthixol, and thiothixene competing for binding with the expected stereospecificity. Antagonists such as haloperidol, chlorpromazine, phentolamine, and propranolol inhibited binding. Agonists such as apomorphine, dopamine, epinephrine, norepinephrine, clonidine, and isoproterenol competed with dihydroergocryptine binding, exhibiting potency parallel to their ability to inhibit prolactin release in rat anterior pituitary cells. Ergot alkaloids inhibited prolactin release, whereas phenothiazines, thioxanthenes, and butyrophenones reversed the dopamine-induced inhibition of prolactin release. Anterior pituitary dopaminergic receptors may play a role in the control of prolactin secretion. (Journal abstract modified)

001983 Carruba, Michele O.; Picotti, Giovanni B.; Zambotti, Fernanda; Mantegazza, Paolo. Istituto di Farmacologia, Facolta di Medicina, Universita di Milano, Via Vanvitelli 32, I-20129 Milano, Italy **Effects of mazindol, fenfluramine and chlorimipramine on the 5-hydroxytryptamine uptake and storage mechanisms in rat brain: similarities and differences.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 300(3):227-232, 1977.

Similarities and differences in the effects of mazindol, fenfluramine, and chlorimipramine on the 5-hydroxytryptamine (5-HT) uptake and storage mechanisms in rat brain were identified. It was found that mazindol and fenfluramine inhibited in vitro the uptake of 5-HT into rat forebrain synaptosomes, whether the synpatosomes were incubated in vitro with the drugs or obtained from animals pretreated in vivo. Chlorimipramine was also effective in this latter preparation. Dose response relationships and time course of this effect for the various drugs were determined. Fenfluramine also caused release of 5-HT from preloaded synaptosomes in in vitro incubations. Brain 5-HT levels were measured after acute and chronic administration of mazindol, fenfluramine and chlorimipramine. Mazindol had no effect; fenfluramine was active in reducing brain 5-HT concentration acutely and chlorimipramine only after chronic administration. It was concluded that even a long-lasting inhibition of the uptake, such as that induced by mazindol, is not sufficient to cause depletion of brain 5-HT. 38 references. (Author abstract modified)

001984 Castellani, Sam A.; Ellinwood, Everett H., Jr.; Kilbey, M. Marlyne. Behavioral Neuropharmacology Section, Dept. of Psychiatry, P.O. Box 3870, Duke Univ. Medical Center, Durham, NC 27710 **Tolerance to cocaine-induced convulsions in the cat.** European Journal of Pharmacology (Amsterdam). 47(1):57-61, 1978.

Tolerance to cocaine-induced convulsions was studied in the cat. Determination of minimum convulsive dose of cocaine, across 13 days in a seizure group (n=6) and on day 14 in a subseizure group (n=6) revealed significant tolerance to cocaine-induced convulsions. However, reverse tolerance to cocaine-induced abnormal behavior developed as dystonic posture and speed of stereotyped movement increased during the 13 day treatment period in the subseizure group. These data are discussed in terms of the local anesthetic and catecholaminergic effects of cocaine, as well as possible differential effects of various routes of administration. 28 references. (Author abstract modified)

001985 Chan, Samuel H. H.; Lee, C. M.; Wong, Patrick C. L. Department of Physiology, Faculty of Medicine, University of Hong Kong, Hong Kong **Suppression of caudate neuron activities by morphine and the involvement of dopaminergic neurotransmission.** Federation Proceedings. 36(3):395, 1977.

Effects of morphine on spontaneous activity in the caudate nucleus in rats anesthetized with pentobarbital were reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Three to five min after intracarotid injection of morphine, spontaneous discharges of single caudate neurons were totally suppressed; this suppression was reversed by naloxone intracarotid. Morphine suppression did not occur in rats pretreated with haloperidol or pimozide. Morphine excited 60% of substantia nigral neurons studied, while electrical stimulation of the substantia nigra suppressed 40% of caudate neurons. The release of dopamine by the nigrostriatal pathway may be involved in the suppression of caudate neurons. (Journal abstract modified)

001986 Chance, William T.; Krynock, Glenn M.; Rosecrans, John A. Dept. of Pharmacology, Medical College of Virginia, Virginia Commonwealth Univ., MCV Station, Box 726, Richmond, VA 23298 **Effects of medial raphe and raphe magnus lesions on the analgesic activity of morphine and methadone.** Psychopharmacology (Berlin). 56(2):133-137, 1978.

The effects of lesions of the raphe nuclei on opiate-induced antinociception and brain serotonin (5-HT) levels were investigated. Lesions of the medial raphe nucleus effectively antagonized the analgesic effects of morphine, but not methadone, and lowered brain 5-HT. The decrement in analgesic activity of morphine was reversed by pretreatment with 5-hydroxytryptophan. Lesions of the raphe magnus, a descending 5-HT system, antagonized the analgesic potency of both morphine and methadone. These experiments indicate a differential effect of 5-HT manipulation on opiate-induced analgesia, suggesting a different mechanism of analgesic action for morphine and methadone. 25 references. (Author abstract)

001987 Chanda, S. K.; McCreedy, S.; Morgan, M. Pennwalt Pharmaceutical Division, Rochester, NY 14623 **In vivo effects of tricyclic antidepressants on biogenic amine uptake in rat brain.** Federation Proceedings. 36(3):327, 1977.

Effects of doxepin and imipramine on the uptake of catecholamines and serotonin in synaptosomal fractions of the hypothalamus and corpus striatum of rat brain will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Both drugs inhibitied norepinephrine and dopamine uptake in the hypothalamus, but serotonin uptake was not affected. Catecholamine uptake in the corpus striatum was unaffected. The inhibitory effects of imipramine were more pronounced than those of doxepin. (Journal abstract modified)

001988 Chen, H. T.; Simpkins, J. W.; Mueller, G. P.; Meites, J. Neuroendocrine Research Laboratory, Department of Physiology, Michigan State University, East Lansing, MI 48824 **Effects of pargyline on hypothalamic biogenic amines and serum prolactin (PRL), LH and TSH in male rats.** Federation Proceedings. 36(3):366, 1977.

Effects of pargyline on biogenic amines in the hypothalamus and on serum levels of prolactin, luteinizing hormone (LH), and thyrotropin (TSH) in adult male rats will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Pargyline was injected into rats, and they were sacrificed 1, 2, 4, or 6 hr later. Hypothalamic dopamine concentrations were found to be 79% higher at 1 hr, and then gradually declined; norepinephrine increased 31% at 1 to 6 hr; serotonin increased from 42% at 1 hr to 95% at 6 hr; prolactin, LH, and TSH were decreased at 2 hr, but returned to normal by 4 hr; and at 6 hr, prolactin was increased fourfold, but LH and TSH were at normal levels. The inhibitory effects of pargyline on the three hormones at 2 hr seem to be due to the acute increase in dopamine, while the stimulatory effect of pargyline on prolactin at 6 hr seems to be due to the increase in serotonin. (Journal abstract modified)

001989 Cheramy, A.; Nieoullon, A.; Glowinski, J. Groupe NB, INSERM U. 114, College de France, F-75231 Paris Cedex 05, France **Blockade of the picrotoxin-induced in vivo release of dopamine in the cat caudate nucleus by diazepam.** Life Sciences (Oxford). 20(5):811-816, 1977.

Effect of diazepam on spontaneous and picrotoxin evoked release of dopamine in the caudate nucleus of the cat was studied. A push pull cannula was introduced stereotaxically into the left caudate nucleus of an encephale isole animal and tritiated tyrosine in artificial cerebrospinal fluid was introduced. The tritiated dopamine endogenously synthesized and released in the superfusate was separated by chromatography and measured in a scintillation counter. Picrotoxin markedly enhanced the release of synthesized tritiated dopamine. Diazepam had no effect alone on the release of tritiated dopamine, but when given 1 hr before picrotoxin it prevented the stimulating effect of picrotoxin on tritiated dopamine release. When given 2 hr after picrotoxin, diazepam progressively reversed the stimulatory effect of picrotoxin on tritiated dopamine release in the caudate nucleus. EEG seizures induced by picrotoxin were prevented or blocked by diazepam. 23 references.

001990 Clemens, James A.; Smalstig, E. B.; Fuller, R. W. Lilly Research Laboratories, Indianapolis, IN 46206 **Effects of complete hypothalamic deafferentation and 5,7-dihydroxytryptamine on several parameters of prolactin release.** Federation Proceedings. 36(3):277, 1977.

An investigation of the serotonergic basis of prolactin secretion in rats was presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. 5-Hydroxytryptophan or fluoxetine, a serotonin uptake inhibitor, when given alone to normal female rats had no effect on prolactin levels. In rats pretreated with fluoxetine, however, administration of 5-hydroxytryptophan caused an increase in serum prolactin levels. In rats in which the hypothalamus had been deafferented, the same doses of fluoxetine and 5-hydroxytryptophan caused an even greater release of prolactin, suggesting that one group of serotonin neurons controlling prolactin release lies within the hypothalamus. In female rats pretreated with desipramine, intraventricular administration of 5,7-dihydroxytryptamine had no effect on ability to release prolactin at proestrus or during lactation, although brain serotonin levels were 35% of control levels. The rise in serum prolactin levels on the afternoon of estrus was completely obliterated after 5,7-dihydroxytryptamine, suggesting that serotonin neurons control the afternoon elevation of prolactin. (Journal abstract modified)

001991 Codd, E. E.; King, C. D.; Byrne, W. L. Department of Biochemistry, University of Tennessee Center for the Health Sciences, Memphis, TN 38163 **Multiple classes of opiate receptors in C57BL/6J and DBA/2J mouse brain.** Federation Proceedings. 36(3):845, 1977.

An investigation of the binding of tritiated dihydromorphine and naltrexone to washed mouse brain homogenates was reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. The number of naltrexone binding sites equaled the sum of the number of the two apparent dihydromorphine sites. When naltrexone binding was measured in the presence of Na ion, the apparent number of naltrexone binding sites was increased 50%. Double reciprocal plots of inhibition curves indicate a more complex situation than simple competitive inhibition. All the sites occupied by naltrexone were accessible to both agonist and antagonist, while not all the sites occupied by dihydromorphine were accessible to even another agonist. There seems to be more than one kind of opiate receptor. Partially purified endorphin displaced tritiated dihydromorphine or naltrexone from all sites. (Journal abstract modified)

001992 Coil, Janet D.; Hankins, Walter G.; Jenden, Donald J.; Garcia, John. Neuropsychiatric Institute, 760 Westwood Plaza, Los Angeles, CA 90024 **The attenuation of a specific cue-to-consequence association by antiemetic agents.** Psychopharmacology (Berlin). 56(1):21-25, 1978.

To test the hypothesis that the expression of a taste aversion may reflect classically conditioned nausea mediated by activation of brainstem emetic centers by taste stimuli, rats were allowed to drink a saccharin solution and 10 min later were intubated with LiCl to produce nausea. When control rats were posttested for saccharin preference they consumed less than 50% of their pretest intake. Experimental rats were injected with one of four pharmacologically distinct antiemetic drugs 30 min prior to their posttest with saccharin. Each drug significantly attenuated the aversion to saccharin at one dose level. The antiemetic drugs used were scopolamine HBr, cyclizine, prochlorperazine dimaleate, and trimethobenzamide. These drugs had no effect on the conditioned fear of a noise that signaled foot shock or on a natural aversion to a bitter fluid. Data suggest that pharmacological suppression of the neural mechanisms of emesis selectively disrupts conditioned taste aversions, and that moderate dose levels are critical for obtaining this effect. 25 references. (Author abstract modified)

001993 Cooper, Barrett R.; Boyer, Charles E. Dept. of Pharmacology, Wellcome Research Laboratories, Research Trian-

gle Park, NC 27709 **Stimulant action of thyrotropin releasing hormone on cat spinal cord.** Neuropharmacology (Oxford). 17(2):153-156, 1978.

A series of studies were undertaken to further explore the stimulant action of thyrotropin releasing hormone (TRH) on cat spinal cord. TRH produced a rapid dose related elevation of muscle tonus accompanied by tremor and shivering-like movements in cats. This stimulant action of TRH also occurred in decerebrate cats and cats which had undergone spinal cord transection at the level of the first cervical vertebra. Recordings from spinal cord ventral roots indicated that TRH induced a pronounced increase in spontaneous motor neuron action potentials. No such stimulation of muscle activity was produced by injections of thyrotropin (TSH), triiodothyronine (T3), deamidated TRH, or the constituent amino acids of TRH, pyroglutamic acid, histidine, and proline amide. Results suggest that TRH can act directly on the spinal cord to stimulate muscle activity via a nonendocrine mechanism. 11 references. (Author abstract modified)

001994 Coscia, C. J.; Burke, W.; Jamroz, G.; Kosloff, A.; McFarlane, J.; Mitchell, J.; Wilson, M. L. St. Louis University School of Medicine, St. Louis, MO 63104 **Occurrence of a new class of tetrahydroisoquinolines in L-dopa treated parkinsonian patients.** Federation Proceedings. 36(3):804, 1977.

Aberrant metabolism of dopa to form a new type of tetrahydroisoquinoline alkaloid in parkinsonian patients on L-dopa or L-dopa-carbidopa was reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. In patients under L-dopa therapy the tetrahydroisoquinolines norlaudanosoline carboxylic acid and its 3′-O-methyl ether were present in the urine. Both substances were absent from controls. Comparable excretion data were obtained in rats on the same regimen. When dopamine and 3,4-dihydroxyphenylpyruvate were incubated under physiological conditions, norlaudanosoline carboxylic acid was obtained. When rats were pretreated with carbidopa and injected i.p. with tritiated L-dopa, tritiated norlaudanosoline carboxylic acid 3′-O-methyl ether accumulated in the gut. Catechol-O-methyltransferase methylated 3,4-dihydroxyphenylpyruvate at rates comparable with those of 3,4-dihydroxybenzoate. Thus, methylation may precede condensation in the formation of norlaudanosoline carboxylic acid 3′-0-methyl ether in vivo. (Journal abstract modified)

001995 Creese, Ian; Manian, Albert A.; Prosser, Timothy D.; Snyder, Solomon H. Department of Pharmacology, Johns Hopkins University School of Medicine, Baltimore, MD 21205 **3H-haloperidol binding to dopamine receptors in rat corpus striatum: influence of chlorpromazine metabolites and derivatives.** European Journal of Pharmacology (Amsterdam). 47(3):291-296, 1978.

A series of chlorpromazine metabolites and derivatives was assayed for their ability to compete with (3H)haloperidol binding to dopamine receptors in membranes of rat corpus striatum. 3-Hydroxylation of chlorpromazine doubles affinity for receptor sites, while 7-hydroxychlorpromazine has a potency similar to that of chlorpromazine itself. Other patterns of hydroxylation reduce affinity. Side chain demethylation lowers affinity for binding sites. Several metabolites which lack neuroleptic activity in vivo, such as chlorpromazine-5-oxide, also are inactive in competing for (3H)haloperidol binding. Since blood levels of 7-hydroxychlorpromazine tend to be similar to those of chlorpromazine itself in patients, these observations indicate that 7-hydroxychlorpromazine may account for a major portion of the antischizophrenic efficacy of chlorpromazine. The structure/activity relationships observed in the present study support a model in which chlorpromazine interacts with dopamine receptors by assuming a conformation with its side chain tilted toward ring A. 22 references. (Author abstract)

001996 Creese, Ian; Schneider, Robert; Snyder, Solomon H. Dept. of Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine, Baltimore, MD 21205 **3H-Spiroperidol labels dopamine receptors in pituitary and brain.** European Journal of Pharmacology (Amsterdam). 46(4):377-381, 1977.

The properties of dopamine receptors in brain and pituitary as labeled in vitro with 3H-spiroperidol are described. 3H-Spiroperidol of high specific radioactivity labels receptors in membranes of bovine caudate nucleus and anterior pituitary. The saturation and kinetic properties of 3H-spiroperidol binding are similar in the two tissues. In both caudate and pituitary, 3H-spiroperidol displays very high affinity with a dissociation constant of 0.2to 0.3nM. The relative potencies of numerous dopamine agonists and antagonists in competing for 3H-spiroperidol binding are closely similar in anterior pituitary and caudate. 10 references. (Author abstract modified)

001997 Crews, F. T. Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109 **In vitro effects of desmethylimipramine on the uptake and metabolism of 3H-norepinephrine in rat brain slices.** Federation Proceedings. 36(3):327, 1977.

Metabolism and retention of tritiated norepinephrine in rat brain slices in the presence of varying concentrations of desipramine were reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Slices of hypothalamus, brainstem, parietal cortex, and caudate nucleus were incubated with tritiated norepinephrine for 10 min. The norepinephrine retained in slices from all four regions was much greater than that metabolized to 3,4-dihydroxyphenylglycol, 3,4-dihydroxymandelic acid, 3-methoxy-4-hydroxyphenylglycol, and vanillylmandelic acid. The major metabolite in all four brain areas was 3,4-dihydroxyphenylglycol. In all areas except the caudate nucleus, desmethylimipramine decreased the formation of deaminated metabolites. All brain areas showed a dose dependent decrease in norepinephrine retention. Normetanephrine was increased at the highest desipramine concentration and remained unchanged at lower desipramine concentrations. (Journal abstract modified)

001998 Czarnecka, Elzbieta; Kocur, Jozef; Rydzynski, Zdzislaw. Katedra Farmakologii AM, ul. Narutowicza 120A, 90-145 Lodz, Poland /**Effects of benzydamine on the bioelectric activity of the rabbit brain.**/ Badania nad wplywem benzydaminy na czynnosc bioelektryczna mozgu krolika. Psychiatria Polska (Warszawa). 11(1):15-21, 1977.

Studies on the effects of benzydamine (Benalgin-Polfa) on the bioelectric activity of the rabbit brain are presented based on experiments conducted on 42 rabbits implanted with electrodes. It was found that benzydamine causes changes, both in behavior and in EEG recordings of rabbits, indicative of its stimulating effect on the CNS, particularly on the subcortical structures. Diazepam had no effect on the behavioral and bioelectric changes caused by benzydamine, while haloperidol and reserpine had an inhibitory effect on the intensity and duration of changes in the EEG and behavior of the animals. The results suggest that catecholamines and particularly dopamine may play a role in the mechanism of CNS action of benzydamine. 12 references. (Journal abstract modified)

001999 Dalterio, S.; Bartke, A.; Burstein, S. Worcester Foundation for Experimental Biology, Shrewsbury, MA 01545 **Cannabinoids inhibit testosterone secretion by mouse testes in vitro.** Science. 196(4297):1472-1473, 1977.

The effects of cannabinoids in the inhibition of testosterone secretion by mouse testes in vitro was studied. Laboratory mice were killed by cervical dislocation and the testes removed, decapsulated and incubated in Krebs-Ringer bicarbonate buffer, glucose and human chorionic gonadotropin. Delta9-tetrahydrocannabinol (THC) or cannabinol (CBN) was added to the incubation medium and the amount testosterone determined by radioimmunoassay. Addition of THC or CBN caused a significant reduction in the accumulation of testosterone in the medium. The results suggest that the sexual and reproductive function may result from direct inhibition of testicular steroidogeneses by both psychoactive and nonpsychoactive constituents of marihuana. 20 references. (Author abstract modified)

002000 Davison, A. N. Miriam Marks Dept. of Neurochemistry, Institute of Neurology, National Hospital, Queen Square, London WC1N 3BG, England **The biochemistry of brain development and mental retardation: the Eleventh Blake Marsh Lecture delivered before the Royal College of Psychiatrists, 7 February, 1977.** British Journal of Psychiatry (London). 131:565-574, 1977.

Biochemical and morphological changes which occur under experimental conditions and produce permanent behavioral changes in animals are examined and this information is interpreted in terms of the neuropathology of mental retardation. Focus is given to the effect of undernutrition, lead poisoning, and exposure to neuroactive drugs during a critical period of brain development. Possible biochemical mechanisms operating in these various conditions and in animal models are reviewed in relation to the vulnerable period hypothesis. It is suggested that small brains are common in the mentally retarded, and that this may be related to a developmental abnormality particularly at the level of the synapse. 61 references. (Author abstract modified)

002001 De Montis, Graziella M.; Olianas, Maria C.; Di Lorenzo, Carla; Tagliamonte, Alessandro. University of Cagliari, Via Porcell 4, I-09100 Cagliari, Italy **Failure of morphine to increase striatal 3,4-dihydroxyphenylacetic acid in fasted rats.** European Journal of Pharmacology (Amsterdam). 47(1):121-123, 1978.

The effect of morphine on striatal 3,4-dihydroxyphenylacetic acid in fasted rats was studied. Results indicate that morphine given to rats fed ad libitum increased the striatal levels of dopamine and 3,4-dihydroxyphenylacetic acid, while naloxone had no effect. Conversely, after prolonged fasting, morphine failed to increase both dopamine and 3,4-dihydroxyphenylacetic acid, while naloxone markedly decreased striatal 3,4-dihydroxyphenylacetic acid concentration. Intermediate sensitivity to 3,4-dihydroxyphenylacetic acid increasing effect of morphine and to 3,4-dihydroxyphenylacetic acid decreasing effect of naloxone was present in rats trained to eat their daily meal within 2 hours, at different times after feeding. These findings suggest that striatal dopamine synthesis in fasted rats is sustained by an increased endorphin-like activity. 6 references. (Author abstract modified)

002002 Di Chiara, G.; Porceddu, M. L.; Vargiu, L.; Stefanini, E.; Gessa, G. L. Institute of Pharmacology, University of Cagliari, Via Porcell, I-09100 Cagliari, Italy **Evidence for selective and long-lasting stimulation of "regulatory" dopamine-receptors by bromocriptine (CB 154).** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 300(3):239-245, 1977.

The effects of bromocriptine (CB-154), an ergot derivate with dopamine (DA) stimulating properties in vivo, on dopamine receptors in rat brain were investigated. Bromocriptine produced long-lasting hypomotility in mice unaccustomed to the motility cage and decreased brain 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) without affecting brain DA. Decrease of brain DOPAC was correlated to the hypomotility on both a dose and a time basis. Potent neuroleptics pimozide, benzperidol and droperidol, antagonize the hypomotility and the decrease of brain DOPAC produced by bromocriptine. These effects were obtained with very low doses (0.05 to 0.3mg/kg) of neuroleptics which per se did not affect motility or brain DOPAC. The maximal decrease of brain DOPAC and HVA produced by bromocriptine was similar to that produced by apomorphine and the combination of these drugs did not result in a further decrease of brain DOPAC or HVA. On the basis of these results it is postulated that bromocriptine decreases brain DA turnover and produces hypomotility by acting on regulatory DA receptors different from the postsynaptic ones of the terminal dopaminergic areas. 37 references. (Author abstract modified)

002003 Dingledine, Raymond; Iversen, Leslie L.; Breuker, Ellen. Nevrofysiologisk Institutt, University of Oslo, Karl Johans gt. 47, Oslo 1, Norway **Naloxone as a GABA antagonist: evidence from iontophoretic, receptor binding and convulsant studies.** European Journal of Pharmacology (Amsterdam). 47(1):19-27, 1978.

Evidence from iontophoretic, receptor binding, and convulsant studies concerning naloxone as a GABA antagonist is presented. Iontophoretic naloxone reversibly antagonized GABA evoked depression of firing rate in 21 of 27 neurons tested in the rat olfactory tubercle nucleus accumbens region, without blocking inhibition evoked in the same cells by glycine (15 cells) or morphine (6 cells). Naloxone in high doses caused convulsions in mice and potentiated the convulsant activity of bicuculline, but not that of strychnine. Diazepam, which protected mice against convulsions elicited by bicuculline, but not by strychnine, also protected mice against naloxone. Naloxone, morphine, levorphanol and its nonanalgesic enantiomer dextrorphan displaced (3H)GABA from receptor sites in rat forebrain and cerebellum, with similar low potency. On the basis of this evidence, it is proposed that at least part of the convulsant activity of naloxone is a result of GABA receptor blockade. 33 references. (Author abstract modified)

002004 Divinetz-Romero, S.; Richelson, E. Department of Psychiatry, Mayo Foundation, Rochester, MN 55901 **Antidepressant drugs block muscarinic acetylcholine receptor mediated formation of cyclic GMP in cultured mouse neuroblastoma cells.** Federation Proceedings. 36(3):290, 1977.

The ability of tricyclic antidepressants to block the muscarinic receptor in mouse neuroblastoma cells will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Cyclic GMP formation was measured in clone N1E-115 by radioactively labeling intracellular stores of GTP. Antidepressants caused parallel displacement of the dose response curves for carbamylcholine, indicating competitive inhibiton. Equilibrium dissociation constants determined from the shift in the dose/response curves separated the drugs into two groups: amitriptyline, imipramine, chlorimipramine, and doxepin in one group and protriptyline, nortriptyline, and desipramine in the other group. Results indicate that tricyclic drugs with terti-

ary amine side chains are about tenfold more potent in blocking the muscarinic receptor than are those with secondary amine side chains. (Journal abstract modified)

002005 Dolphin, Annette; Enjalbert, Alain; Tassin, Jean-Paul; Lucas, Marguerite; Bockaert, Joel. Laboratoire de Physiologie Cellulaire, College de France, 11 place Marcelin Berthelot, F-75231 Paris Cedex 05, France **Direct interaction of LSD with central "beta"-adrenergic receptors.** Life Sciences (Oxford). 22(4):345-351, 1978.

The interaction of (+)-lysergic acid diethylamide (LSD) with central beta-adrenergic receptors, both in the cerebral cortex of the rat and in cultured C6 glioma cells is reported. LSD inhibited the binding of (3H)dihydroalprenolol (3HDHA) with an apparent inhibition constant of 10-7M in the cerebral cortex and 10-6M in C6 glioma cells. The displacement of 3HDHA binding by LSD was found to be competitive in the cortex. BOL, an analogue of LSD without hallucinogenic properties, showed the same affinity as LSD for the cortical beta-adrenergic receptor. However, several dopamine and serotonin agonists and antagonists were without effect at 10-6M. The stimulation of adenylate cyclase by isoproterenol was inhibited by LSD. The results suggest that central beta-adrenergic receptors represent one of the several sites of action of LSD. 21 references. (Author abstract modified)

002006 Donoso, A. O. Instituto de Investigaciones Cerebrales, Facultad de Ciencias Medicas, Universidad Nacional de Cuyo, Mendoza, Argentina **Blockage of progesterone-induced release of luteinizing hormone and prolactin by d-amphetamine and fenfluramine in rats.** Psychopharmacology (Berlin). 55(2):173-176, 1977.

To examine the effects of d-amphetamine and fenfluramine on plasma luteinizing hormone (LH) and prolactin (PRL) secretion, various doses of d-amphetamine or fenfluramine were administered to ovariectomized or ovariectomized plus estradiol or progesterone treated rats. D-amphetamine at 1.25, 2.5, and 5mg/kg decreases plasma LH levels in estradiol plus progesterone treated rats. In these animals PRL levels decrease after injection of 0.6and 1.25mg/kg amphetamine. No significant hormone modifications were found in ovariectomized or ovariectomized estradiol primed rats after 2.5mg/kg d-amphetamine. Fenfluramine at doses of 25mg/kg induces decreases of plasma LH and PRL in estradiol and progesterone treated rats; while 2.5mg/kg has no effect. Results suggest that d-amphetamine and fenfluramine are able to alter the facilitatory actions of progesterone on LH and PRL release in ovariectomized estradiol primed rats. 32 references. (Author abstract modified)

002007 Eisenhardt, Rudolf H.; Levin, Sidney S.; Touchstone, Joseph C.; Cooper, David Y. Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania, Philadelphia, PA 19174 **Phenobarbital metabolism during chronic administration in rats.** Federation Proceedings. 36(3):844, 1977.

A study of the metabolic fate of (C14)phenobarbital administered daily to rats, followed in the urine, feces, serum, and exhaled carbon dioxide, was reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Although radioactive carbon dioxide accounted for only a small fraction of total radioactivity, the time sequence of its appearance followed that established for the induction pattern of cytochrome-P-450 hydroxylation. C14 Labeled carbon dioxide first appeared after the third daily phenobarbital injection, and its concentration was highest in the hours immediately following each injection. C14 serum levels one half hour after each injection accounted for 5% of the newly injected C14, but less than 0.5% remained in circulation 23 1/2 hr later. Some 65% of each day's added radioactivity was present in the 24 hr urine collections, and almost all the rest of the radioactivity appeared in the feces, mostly as hydroxylated and conjugated phenobarbital. Bile cannulation showed that much of the drug passed unchanged via the bile duct into the intestines with little hydroxylated phenobarbital being present, but conjugated phenobarbital was found. Bile results suggest a contribution of intestinal bacteria to phenobarbital metabolism. (Journal abstract modified)

002008 Enz, A.; Iwangoff, P.; Chappuis, A. Basic Medical Research Department, Sandoz Ltd., CH-4002 Basel, Switzerland **The influence of dihydroergotoxine mesylate on the low-Km phosphodiesterase of cat and rat brain in vitro.** Gerontology (Basel). 24(Supplement 1):115-125, 1978.

In a paper presented at a workshop on advances in experimental pharmacology of hydergine in Basel, December 1976, a report of a study on the influence of dihydroergotoxine mesylate on purified particulate low affinity (low Km) phosphodiesterase of cat and rat brain in vitro is given. Dihydroergotoxine mesylate (DHET) was found to be a stronger inhibitor of the low-Km than of the high-Km phosphodiesterase (PE) in cat and rat brain homogenates. The inhibition due to DHET was greater when a purified low-km PE preparation originating from a sonicated pellet (100,000 g) of rat brain tissue was used. It was also found that the drug alters the kinetic properties of the enzyme, producing a lowering of the negative cooperativity effect. This kind of PE inhibition is of particular importance at normal cellular cAMP levels, but does not interfere with cAMP production by hormonal stimulation. 16 references. (Author abstract modified)

002009 Erwin, David N.; Nonchoji, Toshiaki; Wood, Jackie D. Department of Physiology, University of Kansas Medical Center, Kansas City, KS 66103 **Effects of morphine on electrical activity of single myenteric neurons in cat small bowel.** European Journal of Pharmacology (Amsterdam). 47(4):401-405, 1978.

A study of morphine effects on the discharge of single myenteric neurons in the cat small intestine is reported. Quantitative parameters of the discharge patterns of burst type units and single spike units were increased, decreased or unchanged after application of morphine. The results were the same when morphine was added in the presence of naloxone. The results suggest that morphine had no consistent effect on the spike discharge of continuously active neurons in Auerbach's plexus of cat small intestine. 22 references. (Author abstract modified)

002010 Feldman, Stuart; Putcha, Lakshmi. Dept. of Pharmaceutics, College of Pharmacy, University of Houston, Houston, TX 77004 **Effect of anti-parkinsonism drugs on gastric emptying and intestinal transit in the rat.** Pharmacology (Basel). 15(6):503-511, 1977.

The effect of atropine sulfate, trihexyphenidyl HCl, benztropine mesylate, diphenhydramine HCl and ethopropazine HCl on gastric emptying and intestinal transit of a phenol red solution in the rat was examined. Intraperitoneal administration of 0.3mg/kg atropine, 1.2mg/kg benztropine and trihexyphenidyl results in a marked decrease in gastric emptying and intestinal transit rate when compared to controls. Oral administration of these agents produced variable and unpredictable results. Single and multiple oral dose (0.6to 3mg/kg) studies

with trihexyphenidyl failed to produce any significant decreases in gastric emptying rates. A single oral dose of benztropine (0.6to 3mg/kg) failed to reduce the gastric emptying rate, but multiple dose studies produced a significant decrease in the gastric emptying rate. Effects on gastric emptying and intestinal transit were seen after single and multiple oral doses of diphenhydramine and ethopropazine. Results indicate the possibility of reduced L-dopa bioavailability when combined with antiparkinsonian drugs and of an alteration in gastrointestinal absorption of other drugs. Gastrointestinal drug absorption interactions still require more investigation to assess the therapeutic importance of the observed effects. 19 references. (Author abstract modified)

002011 Ferri, Sergio; Arrigo-Reina, Rosa; Scoto, Giovanna Maria; Giagnoni, Gabriella; Marsi, Adriana; Santagostino, Angela. Institute of Pharmacology, Faculty of Pharmacy, Univ. of Catania, Catania, Italy **Effect of maternal morphine administration on fetal and neonatal rat liver tyrosine aminotransferase.** Biochemical Pharmacology (Oxford). 27(2):249-250, 1978.

The effects of acute and chronic maternal morphine administration on fetal and neonatal rat liver tyrosine aminotransferase (TAT) were investigated. Morphine influences corticosteroid secretion: single doses of the narcotic generally stimulate adrenal responses whereas prolonged administration produces depression of the basal levels of corticosteroid secretion. The mechanism by which morphine influences corticosteroid secretion is not clearly defined, but evidence suggests that it could act at a central site, probably through the stimulation and inhibition of the synthesis or output of releasing factor(s) responsible for the control of the pituitary adrenal system. It is hypothesized that increased adrenal activity occurs in rats newly born to morphine treated mothers due to a sudden lack of maternal supplied morphine, with a consequent stimulus of TAT synthesis. 11 references.

002012 Fink, John Stephen. Cornell University Medical College, New York, NY **Studies on the role of forebrain catecholamine neurons in exploratory behavior in the rat. (Ph.D. dissertation).** Dissertation Abstracts International. Ann Arbor, MI, Univ. M-films, No. 77-25059 HC$15.00 MF$7.50 286 p.

To examine the role of specific catacholamine (CA) terminal fields in locomotor and investigatory exploration, rats were microinjected with 6-hydroxydopamine (6-OHDA) at two sites along the medial forebrain bundle in the anterior hypothalamus and into the nucleus accumbens and the anteromedial caudate. Effects of chlorpromazine, clonidine, 1-DOPA, and apomorphine on 6-OHDA-induced deficits were also investigated. Results of studies indicate: 1) dopaminergic afferents from mesencephalon to mesolimbic, mesocortical, and anteromedioventral striatal terminal fields are necessary to normal locomotor and investigatory exploration; 2) noradrenergic afferents to neocortex, hippocampus, piriform cortex, and anteromedial hypothalamus are not necessary to these behaviors in some tasks; and 3) systemic administration of low doses of apomorphine after ablation of dopaminergic afferents to limbic forebrain and anteromedioventral striatum permits normal locomotor and investigatory exploration of novel stimuli, suggesting that afferents to these areas may subserve a similar permissive function in the intact rat brain. (Journal abstract modified)

002013 Fjalland, B. Dept.of Pharmacology & Toxicology, H. Lundbeck & Co. A/S, Ottiliavej 7-9, DK-2500 Copenhagen, Denmark **Inhibition by neuroleptics of uptake of 3H-GABA into rat brain synaptosomes.** Acta Pharmacologica et Toxicologica (Kobenhavn). 42(1):73-76, 1978.

Neuroleptics and some amino acids were examined for GABA uptake inhibiting properties in rat brain synaptosomes. Results indicate that the phenothiazine and thioxanthene neuroleptics inhibited GABA uptake by 50% in the concentration range of 10 to 30 micromoles. No difference in potency was found between the cis-isomers and transisomers of the thioxanthenes. Clozapine and sulpiride were weak inhibitors of the GABA uptake process, whereas some of the butyrophenones examined exhibited rather potent effect. Specific GABA uptake inhibitors were as active as the most potent butyrophenones. As no significant correlation was obtained between GABA uptake inhibiting effect of the neuroleptics and their clinical of pharmacological effect, it is concluded that the influence on GABA uptake is not an important aspect of the neuroleptic action. 18 references. (Author abstract modified)

002014 Frankel, David; Khanna, Jatinder M.; Kalant, Harold; Leblanc, A. Eugene. Dept. of Pharmacology, University of Toronto, Toronto M5S 1A8, Canada **Effect of p-chlorophenylalanine on the loss and maintenance of tolerance to ethanol.** Psychopharmacology (Berlin). 56(2):139-143, 1978.

To study the effect of p-chlorophenylalanine (p-CPA) on tolerance to ethanol, rats were rendered tolerant to the motor impairing effects of ethanol by daily oral administration, and ethanol was subsequently withdrawn and the effect of p-CPA on tolerance loss was examined. In two separate studies it was demonstrated that p-CPA, in a dosage regimen that produces extensive depletion of brain serotonin (5-HT), accelerated tolerance loss. These experiments suggest that at least part of p-CPA's inhibitory effect on net tolerance development to ethanol can be accounted for by its accelerating effect on tolerance loss; however, an inhibitory effect on tolerance acquisition cannot be excluded. On the other hand, once tolerance was established, p-CPA did not affect the maintenance of tolerance to ethanol. 8 references. (Author abstract modified)

002015 Frizza, J.; Chesher, G. B.; Jackson, D. M.; Malor, R.; Starmer, G. A. Dept. of Pharmacology, University of Sydney, N.S.W. 2006, Australia **The effect of delta9-tetrahydrocannabinol, cannabidiol, and cannabinol on the anaesthesia induced by various anaesthetic agents in mice.** Psychopharmacology (Berlin). 55(1):103-107, 1977.

The effect of delta9-tetrahydrocannabinol, cannabidiol, and cannabinol on the anesthesia induced by various anesthetic agents was investigated. Delta9-tetrahydrocannabinol (2.5to 80.0mg/kg) significantly prolonged the anesthesia induced by ketamine, pentobarbitone, thiopentone, propanidid, and Alfathesin in a dose dependent manner. Cannabinol and cannabidiol (both 5.0to 80.0mg/kg) were essentially inactive, except that cannabidiol prolonged pentobarbitone-induced anesthesia. The interaction of delta9-tetrahydrocannabinol with the anesthetic agents was postulated to be due to a centrally mediated action, whereas the effect of cannabidiol on pentobarbitone-induced anesthesia probably depended on a metabolic interaction. The interaction between the cannabinoids in influencing anesthesia induced by the above agents was examined and found to be complex. 25 references. (Author abstract modified)

002016 Fuller, Ray W.; Snoddy, Harold D.; Hemrick, Susan K. Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46206 **Effects of fenfluramine and norfenfluramine on brain serotonin metabolism in rats.** Proceedings of the Society for Experimental Biology and Medicine. 157(2):202-205, 1978.

A series of studies was undertaken to examine the effects of fenfluramine and norfenfluramine on brain serotonin metabolism in rats. Fenfluramine and its N-demethyl metabolite, norfenfluramine (3-trifluoromethyl-amphetamine), lowered brain serotonin, 5-hydroxyindoleacetic acid, and tryptophan hydroxylase in rats acutely and the effect persisted for more than 1 week after a single i.p. dose of the drugs. Serotonin depletion by fenfluramine and norfenfluramine was blocked by pretreatment with fluoxetine, an inhibitor of uptake into serotonin neurons. Serotonin turnover, as measured by the rate of 5-hydroxyindoleacetic acid accumulation after probenecid administration, was decreased significantly still at 1 week after fenfluramine administration. The effects of fenfluramine and norfenfluramine on brain serotonin neurons in rats resemble those of p-chloroamphetamine and probably occur via similar mechanisms. 27 references. (Author abstract modified)

002017 Fuller, Ray W.; Snoddy, Harold D.; Perry, Kenneth W.; Bymaster, Frank P.; Wong, David T. Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN 46206 **Importance of duration of drug action in the antagonism of p-chloroamphetamine depletion of brain serotonin -- comparison of fluoxetine and chlorimipramine.** Biochemcal Pharmacology (Oxford). 27(2):193-198, 1978.

A series of experiments in animals to investigate the influence of pharmacokinetic factors on the action of fluoxetine and chlorimipramine as p-chloroamphetamine (PCA) antagonists is presented. Fluoxetine inhibited both the rapid depletion of brain serotonin by PCA and the ultimate irreversible effects of PCA on brain serotonin neurons in rats. The differences between fluoxetine and chlorimipramine as PCA antagonists appeared to be related to the duration of uptake inhibition by these agents. Fluoxetine given along with PCA in a single dose prevented serotonin depletion at all times after PCA. Chlorimipramine antagonized serotonin depletion initially, but at later times there was little or no protection against PCA effects. The dose dependence of the antagonism of PCA by fluoxetine did not vary greatly with the time of serotonin measurement after PCA, but with chlorimipramine, the effectiveness of a given dose depended markedly on that time interval. Lengthening the pretreatment interval prior to PCA injection from 0 to 16 hr diminished the effectiveness of chlorimipramine but not fluoxetine as antagonists of serotonin depletion. The differences between fluexetine and chlorimipramine may arise primarily because these compounds are metabolized by N-demethylation. The demethylated metabolite of fluoxetine was as potent and specific as fluoxetine itself as a serotonin uptake inhibitor both in vitro and in vivo, whereas the demethylated metabolite of chlorimipramine was less active than chlorimipramine as a serotonin uptake inhibitor and more active as a norepinephrine uptake inhibitor. Chlorimipramine was a more effective PCA antagonist when injected into mice in repeated doses or when injected into rats along with an inhibitor of liver microsomal enzymes. Thus, comparison of uptake inhibitors as antagonists of PCA is strongly influenced by the pharmacokinetics of the drugs involved. 22 references. (Author abstract)

002018 Futami, Takahiro. Household Products Research Lab., Kao Soap Co., Ltd., Bunka, Sumida-ku, Tokyo 131, Japan **Possible involvement of cyclic AMP in inflammation induced by a surfactant.** Japanese Journal of Pharmacology (Kyoto). 27(6):763-767, 1977.

In a study reporting the possible involvement of cyclic AMP in inflammation induced by alkyldimethylbenzylammonium chloride (alkyl DBAC), the mechanism of metabolic changes, consequently the cyclic AMP level and the effects of certain drugs were determined in the gastronemius muscles of rats in which acute exudative inflammation had been induced by intramuscular injections of alkyl DBAC. A transient increase in the cyclic AMP level was noted at 15 to 30 minutes after the injection of alkyl DBAC, and this elevation was antagonized by chlorpromazine, diphenhydramine, promethazine, aspirin, and indomethacin. The time course of increasing tendency in the cyclic AMP level after the injection of histamine closely paralleled that of alkyl DBAC. These results suggest that cyclic AMP may be involved in the metabolic changes with inflammation induced by alkyl DBAC. 31 references. (Author abstract modified)

002019 Fuxe, Kjell; Fredholm, Bertil B.; Agnati, Luigi F.; Corrodi, Hans. Dept. of Histology, Karolinska Institutet, S-10401 Stockholm, Sweden **Dopamine receptors and ergot drugs. Evidence that an ergolene derivative is a differential agonist at subcortical limbic dopamine receptors.** Brain Research (Amsterdam). 146(2):295-311, 1978.

The actions of a new type of ergolene derivative, MPME ((5R, 8R)-8-(4-p- (5R, 8R)-8-(4-p-methoxyphenyl-l-piperazinyl methyl)-6-methylergolene(MPME), were evaluated on central catecholamine (CA) neurons in the rat by means of a combined biochemical, histochemical, and behavioral analysis. The evidence suggests that this ergolene derivative is a preferential agonist at subcortical limbic dopamine (DA) receptors and at DA receptors belonging to the neostriatal DA islands. Drug effects on DA and noradrenaline turnover by time and dose are presented. MPME effects on DA turnover are blocked by haloperidol but not by methergoline. MMPE mimics the behavioral actions of apomorphine, causing prolonged rotational behavior toward the nonoperated side. Results phosphodiesterase and pimozide pretreatment are reported. Also outlined are MMPE effects on adenylate cyclase in the nucleus caudate and subcortical limbic system. Evidence indicates that DA receptor populations in the brain are sufficiently different to allow their preferential activation. 25 references. (Author abstract modified)

002020 Gahwiler, B. H. Biological and Medical Research Division, Sandoz Ltd., CH-4002 Basel, Switzerland **Dihydroergotoxine-induced modulation of spontaneous activity of cultured rat Purkinje cells.** Gerontology (Basel). 24(Supplement 1):71-75, 1978.

In a paper presented at a workshop on experimental pharmacology of hydergine in Basel, December 1976, a study of dihydroergotoxine mesylate (DHET) on the bioelectric activity of cultured cells were studied and interaction with putative neurotransmitters is reported. Nerve tissue culture were used. It was found that DHET modulated the spontaneous activity of cultured neurons. Addition of .00000001g/ml DHET to rat cerebellar explants led to a significant regularization of the spontaneous firing of Purkinje cells. Within the .0000000001 to .00001g/ml concentration range used in these experiments, DHET had no detectable effect on the average firing rate. 12 references. (Author abstract modified)

002021 Gardier, Robert W.; Tsevdos, Estelle J.; Jackson, Daniel B. Wright State University, Dayton, OH 45435 **The effect of pancuronium and gallamine on muscarinic transmission in the superior cervical ganglion.** Journal of Pharmacology and Experimental Therapeutics. 204(1):46-53, 1978.

To examine the effect of pancuronium and gallamine on muscarinic transmission in the superior cervical ganglion, a study was conducted. Pancuronium enhanced contraction of

the nictitating membrane elicited via ganglionic muscarinic pathways in the superior cervical ganglion of the cat. In order to elucidate this phenomenon, recordings of the superior cervical ganglion surface potential were made which demonstrated that pancuronium and gallamine reduced and haloperidol enhanced ganglionic hyperpolarization without significantly altering the ganglionic slow depolarization. Pancuronium reversed the effects produced by haloperidol, whereas the latter drug was unable to antagonize those induced by pancuronium. These results allow the speculation that pharmacologically distinct muscarinic receptors reside in sympathetic ganglia, one of which is susceptible to blockade by pancuronium or gallamine. 19 references. (Author abstract)

002022 Ghosh, S. K.; Guha, S. R. National Institute of Occupational Health, Ahmedabad-380016, Gujaiat, India **Further studies on the inhibition of monoamine oxidation by monoamine oxidase inhibitors.** Biochemical Pharmacology (Oxford). 27(1):112-114, 1978.

A study of the comparative effects of monoamine oxidase (MAO) inhibiting drugs on rat brain monoamine oxidation and monoamine dehydrogenating (MADH) activity which was performed to determine whether the two activities were performed by the same enzyme or by two different enzymes is reported. Intraperitoneal administration of iproniazid, tranylcypromine, pargyline, catron, and nialamide all produced a marked inhibition of MAO activity. The nonhydrazine MAO inhibitors (tranylcypromine and pargyline) had no effect on MADH activity, whereas the hydrazine derivatives (iproniazid, catron, and nialamide) caused a slight inhibition in MADH activity. In vitro studies indicated that the MADH inhibiting effects of the hydrazine derivatives were less than their MAO inhibiting effects and that MADH inhibition was achieved by higher concentrations of the drugs than were needed to achieve MAO inhibition. Tranylcypromine and pargyline failed to inhibit MADH activity in vitro but did inhibit MAO activity. It is suggested that MAO and MADH are separate enzymes. Further study on the role of MADH in monoamine metabolism is urged. 28 references.

002023 Gnegy, M. E.; Lucchelli, A.; Costa, E. Laboratory of Preclinical Pharmacology, NIMH, Saint Elizabeths Hospital, Washington, DC 20032 **Correlation between drug-induced supersensitivity of dopamine dependent striatal mechanisms and the increase in striatal content of the Ca2+ regulated protein activator of cAMP phosphodiesterase.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 301(2):121-127, 1977.

Correlation between drug-induced supersensitivity of dopamine dependent striatal mechanisms and the increase in striatal content of the Ca2+ regulated protein activator of cAMP phosphodiesterase was studied in the rat. Rats were injected daily with haloperidol (1.3micromol/kg) for 10 days. From the second to the ninth day after haloperidol withdrawal, the rats developed supersensitivity to the behavioral affects of apomorphine. Concomitantly, the Ka of dopamine for activation of striatal adenylatecyclase was lowered and the striatal content of the Ca2+ dependent protein that activates cAMP phosphodiestrase was increased. It is suggested that the increase in protein activator content of striatal membranes caused by haloperidol could be a primary factor in causing supersensitivity to the biochemical and behavioral effects of dopamine receptor agonists. 32 references. (Author abstract modified)

002024 Goldstein, M.; Lew, J. Y.; Hata, F.; Lieberman, A. NYU Medical Center, Room H 544, 550 First Avenue, New York, NY 10016 **Binding interactions of ergot alkaloids with monoaminergic receptors in the brain.** Gerontology (Basel). 24(Supplement 1):76-85, 1978.

In a paper presented at a workshop on advances in experimental pharmacology of hydergine in Basel, December 1976, a study is reported in which the interactions of ergot alkaloids and of other drugs with dopamine (DA) and alpha-adrenergic receptors were investigated. It was found that the tested ergot alkaloids inhibit synaptosomal tyrosine hydroxylase activity and reverse the apomorphine elicited inhibition of synaptosomal tyrosine hydroxylase activity. Thus, ergot alkaloids interact as both agonists and antagonists with the presynaptic DA receptors. To determine the effects of ergot alkaloids and of neuroleptics on the alpha-adrenergic receptors in the CNS, their effects on the binding of 3H-dihydroergocryptine and 3H-WB-4101 to cerebral cortical membranes were measured. The displacing potencies of the tested ergot alkaloids and of the neuroleptics indicated that they have a high affinity for the alpha-adrenoreceptors in the CNS. The mechanisms underlying the therapeutic efficacy of mixed agonist/antagonists of DA and alpha-adrenergic receptors in Parkinson's disease and in geriatric disorders were considered. 17 references. (Author abstract modified)

002025 Gothert, M. Pharmakologisches Institut der Universitat Hamburg, Martinistrasse 52, D-2000 Hamburg, Germany **Effects of presynaptic modulators on Ca2+-induced noradrenaline release from cardiac sympathetic nerves.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 300(3):267-722, 1977.

A study was conducted with isolated rabbit hearts to determine whether drugs which interact with presynaptic muscarinic receptors, alpha-adrenoceptors and angiotensin receptors modify the noradrenaline (NA) release in response to 1.8mM CaCl2, and whether these drugs affect the Ca2+ independent release that occurs during perfusion with a solution containing a low Na+ concentration. Methacholine and oxymetazoline decreased and angiotensin II increased the NA release evoked by 1.8mM CaCl2; changes in CaCl2-induced NA release were abolished by the corresponding antagonists atropine, phentolamine, and Sar1, Ile8-angiotensin II, respectively. Phentolamine alone increased NA release, whereas the other two drugs separately had no significant effect. NA release induced by perfusion of the heart with the Ca2+ free solution containing a low Na+ and a high K+ concentration was not affected by any of the drugs. Findings are taken to provide additional evidence for the suggestion that modulation of noradrenaline release induced by activation of presynaptic muscarinic, alpha-adrenergic, and angiotensin receptors is mediated by changes in the availability of Ca2+ ions for stimulus release coupling. 25 references. (Author abstract modified)

002026 Gothert, M.; Lox, H.-J.; Rieckesmann, J.-M. Pharmakologisches Institut der Universitat Hamburg, Martinistrasse 52, D-2000 Hamburg 20, Germany **Effects of butyrophenones on the sympathetic nerves of the isolated rabbit heart and on the postsynaptic alpha-adrenoceptors of the isolated rabbit aorta.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 300(3):255-265, 1977.

Effects of butyrophenones on the sympathetic nerves of the isolated rabbit heart and on the postsynaptic alpha-adrenoceptors of the isolated rabbit aorta were studied in rabbit hearts perfused with Tyrode solution and in isolated rabbit aorta strips contracted with 25 mM KCl. It was found that: 1) butyrophenones (droperidol, haloperidol, and trifluperidol) in-

hibited uptake of exogenous noradrenaline (NA) from perfusion fluid into sympathetic nerves; 2) butyrophenones did not alter spontaneous NA release, while NA release in response to electrical stimulation of postganglionic nerves was enhanced by droperidol; 3) increase in electrically stimulated NA output caused by droperidol was abolished by cocaine; 4) NA output evoked by 80 mM KCl was inhibited by butyrophenones; 5) butyrophenones also decreased the NA output induced by activation of the nicotinic receptors on the terminal sympathetic nerves by acetylcholine in the presence of atropine; 6) concentration response curves of various alpha-adrenoceptor agonists for their increasing effect on tension of rabbit aortic strips were shifted to the right in a parallel fashion by the butyrophenones; and 7) apomorphine and dopamine failed to relax aortic strips contracted with KCl. It is concluded that the inhibition of neuronal uptake of NA by droperidol accounts for the increase in electrically stimulated overflow of NA. 54 references. (Author abstract modified)

002027 Gough, A. L.; Olley, J. E. School of Pharmacology, University of Bradford, Bradford BD7 1DP, England **Catalepsy induced by intrastriatal injections of delta9-THC and 11-OH-delta9-THC in the rat.** Neuropharmacology (Oxford). 17(2):137-144, 1978.

To investigate the role of the extrapyramidal system in the action of delta9-tetrahydrocannabinol (delta9-THC) and its metabolite 11-hydroxy-delta9-THC, the behavioral changes in the rat induced by intracerebral administration into the caudate/putamen and globus pallidus were compared with those of intraperitoneal administration. Intrastriatal injection induced dose dependent catalepsy, the parent compound being more potent than the metabolite. Catalepsy was not induced following intrapallidal injection of either drug. The results suggest that the caudate/putamen could be a specific site in the mediation of catalepsy induced by delta9-THC. Intrastriatal amphetamine attenuated delta9-THC-induced catalepsy whereas intrapallidal amphetamine potentiated the effect indicating a complex interaction with dopaminergic systems in the basal ganglia. Delta9-THC and the central cholinergic stimulant, RX-86 synergize on administration to either area indicating a possible cholinergic involvement in the phenomenon. 44 references. (Author abstract modified)

002028 Graefe, K.-H.; Stefano, F. J. E.; Langer, S. Z. Institut fur Pharmakologie und Toxikologie der Universitat Wurzburg, Versbacher Landstrasse 9, D-8700 Wurzburg, Germany **Stereoselectivity in the metabolism of 3H-noradrenaline during uptake into and efflux from the isolated rat vas deferens.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 299(3):225-238, 1977.

The metabolism of 3H-(-)noradrenaline (NA) and 3H-(+/-)NA was studied in the isolated rat vas deferens either under conditions of uptake or efflux of the amine. Uptake experiments showed that neuronal mechanisms of amine disposition prevail over extraneuronal ones. Thus, most of the 3H-NA formed during incubation with the amine (including O-methylated products) were of neuronal origin. While neuronal uptake exhibited no selectivity, a pronounced stereoselectivity was found for monoamine oxidase as well as for aldehyde reductase and aldehyde dehydrogenase. The rate limiting step for the neuronal efflux of tritium resided either in the net efflux of amine from the storage vesicles (normal tissues) or in the net efflux across the axonal membrane (tissues with the amine metabolizing enzymes inhibited). The effects of cocaine and phenoxybenzamine on the neuronal efflux of tritiated compounds strongly depend on the intraneuronal distribution of the 3H-amine and indicate that cocaine has only one site of action (neuronal uptake), while phenoxybenzamine exerts reserpine-like as well as cocaine-like effects. The neuronal efflux of tritium from normal tissues preloaded with 3H-(-)NA or 3H-(+/-)NA consisted mainly of amine metabolites. These metabolites represent newly formed metabolites resulting from the catabolism of the neuronally stored amine. This catabolism was brought about through the activity of presynaptic enzymes and was stereoselective. 40 references. (Author abstract modified)

002029 Greenberg, David A.; U'Pritchard, David C.; Sheehan, Peter; Snyder, Solomon H. Dept. of Pharmacology and Experimental Therapeutics, Johns Hopkins Univ., Baltimore, MD 21205 **Alpha-noradrenergic receptors in the brain: differential effects of sodium on binding of (3H)agonists and (3H)antagonists.** Brain Research (Amsterdam). 140(2):378-384, 1978.

The differential effects of sodium on binding of (3H)agonists and (3H)antagonists in alpha-noradrenergic receptors in calf brain were studied. Calf brain homogenates were labeled with the agonists (3H)clonidine, (3H)norepinephrine, (3H)epinephrine, and the (3H)antagonist WB-4101 -- 2-((2',6'-dimethoxy)phenoxyethylamino)methylbenzodioxan, and (3H)dihydroergocryptine (DHE). Assays were conducted in the presence and absence of various concentrations of NaCl, KCl, LiCl and other sodium salts. NaCl in low concentrations reduced alpha-receptor binding of clonidine, epinephrine and norepinephrine; similar results were found for lithium. KCl inhibited (3H)agonist binding very weakly. These results may relate to the similar hydrated atomic radii of sodium and lithium. Sodium and lithium also selectively decreased (3H)agonist binding at opiate receptors. Sodium and lithium had little effect on binding of antagonists (3H)WB-4101 and (3H)DHE. Results are discussed and a model is postulated which is consistent with the effects of sodium upon the opiate receptor and opioid peptide synaptic transmission. 18 references.

002030 Groves, Philip Montgomery. University of Colorado, Boulder, CO **Substrates of elementary behavioral plasticity.** Final Report, NIMH Grant MH-19515, 1977. 10 p.

Studies were conducted to understand the neural mechanisms underlying the simple forms of learning, habituation and sensitization. Based upon work carried out on the cat spinal cord as a model system, a theory was formulated by which changes in neuronal activity in the reticular formation of the brainstem to repetitive sensory input could result in the occurrence of habituation or sensitization. The theory was tested by recording neuronal responses to repetitive sensory stimulation in the reticular formation of the locally anesthetized, immobilized rat. An extensive series of lesion experiments was also performed, in an attempt to determine critical sites of mediation of the acoustic startle response. This simple behavioral response was found to show both habituation and sensitization to repetitive acoustic stimuli. A systematic mapping of reticular formation neuronal responses to different modalities of sensory input was carried out, with particular attention toward regions responsive to auditory stimulation. Neuronal mechanisms of action of amphetamine and antipsychotic drugs are discussed, based on studies of changes in neuronal activity in response to various drug treatments, to integrate changes in neuronal brain activity (especially in the basal ganglia and related structures) with the well known behavioral and biochemical effects of amphetamine and related compounds. (Author abstract modified)

002031 Guidotti, A.; Szmigielski, A.; Costa, E. Laboratory of Preclinical Pharmacology, National Institute of Mental Health, Saint Elizabeths Hospital, Washington, DC 20032 **Pharmacological evidence for a link between the cerebellar content of cGMP and that of an endogenous protein kinase inhibitor.** Federation Proceedings. 36(3):408, 1977.

Two inhibitors of protein kinase that have been isolated were discussed at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Type I inhibitor, with a molecular weight of 24,000, selectively and specifically inhibited cyclic-AMP dependent protein kinase, while type II inhibitor, with a molecular weight of 15,000, inhibited every molecular form of protein kinase by competing with various substrates. Harmaline increased cerebellar cyclic-GMP content and decreased the activity of type II inhibitor by 50%, while diazepam decreased cerebellar cyclic-GMP content and doubled the activity of type II inhibitor. The shifts in type II inhibitory activity were independent from changes in synthesis or degradation of endogenous proteins. In the cerebellum, the type II inhibitor of protein kinase may regulate protein phosphorylation mediated by cyclic-GMP dependent protein kinase. 1 reference. (Journal abstract modified)

002032 Gygax, P.; Wiernsperger, N.; Meier-Ruge, W.; Baumann, T. Med. Grundlagenforschung, Sandoz AG, Lichtstrasse, CH-4002 Basel, Switzerland **Effect of papaverine and dihydroergotoxine mesylate on cerebral microflow, EEG, and pO2 in oligemic hypotension.** Gerontology (Basel). 24(Supplement 1):14-22, 1978.

In a paper presented at a workshop on advances in experimental pharmacology of hydergine in Basel, December 1976, research on the effect of papaverine and dihydroergotoxine mesylate on electroencephalograms (EEG) and central nervous system deficiency studied in the cat brain is reported. Using the hypovolemic oligemia model, an experimental blood flow disturbance was simulated in the cat brain. It was shown in N2O/O2-anesthetized animals, that a 30 to 40% reduction in cerebral blood flow, caused by an oligemia-induced drop in blood pressure led to an instability in cerebral electrical activity. In the course of the 2 hour period of oligemia the EEG activity decreased below the normal energy values by about 30 to 50%. This protective action may be related to its regulating effect on CNS catecholamines, since other substances with protective actions also influence catecholamine metabolism. Papaverine, on the other hand, shows a marked vasoactive effect without preventing the breakdown of the EEG activity. In spite of increasing local cerebral blood flow, papaverine has no positive effect on the oligemia-induced decline in cerebral pO2 values. Therefore, it can be concluded from our oligemia experiments that this substance does not improve nutritional blood flow, but rather leads to a shunt perfusion. 12 references. (Author abstract modified)

002033 Harris, Jane E. Emory University, Atlanta, GA 30322 **Beta-adrenergic receptor-mediated cyclic AMP synthesis in broken-cell homogenates of rat brain.** Federation Proceedings. 36(3):346, 1977.

Paper presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977, reports a study aimed at demonstrating beta-adrenergic receptor linked adenylate cyclase in brain fractions. Crude synaptosomal fractions from rat corpus striatum prelabeled with tritiated adenine were used as substrate. Conversion of newly formed labeled ATP to labeled cyclic AMP was assayed. Phosphodiesterase inhibitors and an ATP regenerating system were present in the reaction mixture. Beta-hydroxylated catecholamines led to greater cyclic AMP accumulation than did dopamine. Propranolol blocked the increase in cyclic AMP formation induced by dopamine and norepinephrine, whereas trifluoperazine had no effect. A beta-type cyclase system was also shown in broken cell homogenates of the cerebral cortex and hindbrain. The responsiveness of the cyclase system was not altered by incubation with exogenous ATP, only with endogenously synthesized ATP, suggesting that beta-adrenergic receptor coupled adenylate cyclase exists in a vesicular pool. (Journal abstract modified)

002034 Harris, L. S.; Carchman, R. A.; Martin, B. R. Dept. of Pharmacology, Medical College of Virginia, Richmond, VA 23298 **Evidence for the existence of specific cannabinoid binding sites.** Life Sciences (Oxford). 22(13-15):1131-1137, 1978.

To determine whether specific binding sites for the cannabinoids exist, a series of experiments was undertaken utilizing hepatoma cells in tissue culture and rat brain homogenates. With the hepatoma cells, high affinity, displaceable binding could be demonstrated alone with a high degree of low affinity nonspecific binding. The displaceable binding appears to be associated with the crude nuclear fraction. In the brain it was found that binding is dependent on protein concentration and that a portion of this binding is temperature dependent. Although saturable binding to the total homogenate or crude mitochondrial fraction could not be demonstrated, displaceable binding was observed in the subfraction containing noncholinergic synaptosomes. Finally, some indication of stereospecific binding is described as are some of the problems encountered with this class of compounds. 15 references. (Author abstract modified)

002035 Heikkila, J.; Holbrook, H.; Brown, I. Dept. of Zoology, Scarborough Coll., Univ. of Toronto, West Hill, Ontario M1C 1A4, Canada **Stress-accentuation of the LSD-induced disaggregation of brain polysomes.** Life Sciences (Oxford). 22(9):757-766, 1978.

The effect of psychological stress following drug administration on the LSD-induced disaggregation of brain polysomes was examined. The application of restraint, food deprivation or epinephrine injection markedly accentuated the disaggregation of rabbit brain polysomes to monosomes induced by LSD (25 microgram/kg), whereas no shift of polysomes to monosomes was found with any of these stress treatments alone. LSD when administered intravenously at a very low dose of 1 microgram/kg and combined with the restraint procedure produced a massive brain polysome shift. LSD alone at this dosage did not induce a disaggregation of polysomes. Elevations in plasma corticosteroid levels relative to control were found following LSD administration with or without the stressing procedures. It is concluded that LSD and certain elements of environmental and physiological arousal appear to have a synergistic effect on disrupting the protein synthesis apparatus of brain. 35 references. (Author abstract modified)

002036 Heikkila, Richard E.; Cabbat, Felicitas S.; Mytilineou, Catherine. Mount Sinai School of Medicine, New York, NY 10029 **Studies on the capacity of dita and mazindol to act as releasing agents and uptake inhibitors for 3H-dopamine (DA) and 3H-norepinephrine (NE) in rat brain tissue slices.** Federation Proceedings. 36(3):381, 1977.

Possible activity of two CNS stimulants and anorectic agents, dita and mazindol, on catecholamine uptake or catecholamine release in rat brain slices was discussed at the

61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. In neostriatal tissue slices, dita and mazindol were found to be 5 to 10 times more potent than cocaine in blocking uptake of tritiated dopamine. Both drugs were very weak releasing agents for tritiated dopamine which had previously accumulated, thus differing from amphetamine, which is a potent dopamine releasing agent. In occipital cortex, dita and mazindol were 5 to 10 times more potent than desipramine in inhibiting uptake of tritiated norepinephrine, but were very weak releasers of tritiated norepinephrine. 3 references. (Journal abstract modified)

002037 Hershkowitz, Norman; Raines, Arthur. Dept. of Pharmacology, Georgetown University, Schools of Medicine and Dentistry, Washington, DC 20007 **Effects of carbamazepine on muscle spindle discharges.** Journal of Pharmacology and Experimental Therapeutics. 204(3):581-591, 1978.

To evaluate effects of carbamazepine (CBZ) on muscle spindle discharges, 32 spinal and alpha-chloralose anesthetized cats were prepared for single unit recording from fibers originating in deefferented spindles of the triceps surae muscles. Stretch induced by a 500g weight drop was used to evaluate spontaneous, static stretch, and poststretch spindle activity, while stretch induced by stimulation of the antagonist muscle group was used to evaluate a phasic stretch response. Preparations were monitored from 15 minutes before to 90 minutes after drug administration. CBZ produced a concentration/dependent depression of most aspects of spindle activity at concentrations ranging from approximately 9 to 45 micrograms/ml. Activity during the poststretch period exhibited the greatest sensitivity to CBZ depression, spontaneous and static stretch activity exhibited intermediate sensitivity and phasic responses were relatively insensitive. No difference between Ia and II sensory endings were observed. Spindle depression was evident at concentrations which had no effect on axonal conduction velocity. The possible influence of this peripheral activity of CBZ is discussed with regard to neurotoxicity and use in the treatment of various neuropathological states. 60 references. (Author abstract modified)

002038 Hesketh, J. E.; Kinloch, N.; Reading, H. W. Centre de Neurochemie, 11 rue Humann, F-67085 Strasbourg, France **The effects of lithium on ATPase activity in subcellular fractions from rat brain.** Journal of Neurochemistry (Oxford). 29(5):883-894, 1977.

The effects of lithium chloride in vitro and in vivo were investigated on Na-K ATPase and Mg ATPase activities in synaptic plasma membrane, mitochondrial and synaptic vesicle fractions prepared from rat brain. In vitro, lithium chloride has no effect on ATPase activity in any of the fractions studied. Lithium chloride given chronically by intraperitoneal injection (30mg/rat/day) for 9 days has little effect on synaptic plasma membrane ATPases. Dietary administration of lithium chloride (60mmol/kg food) produces a small but significant increase in synaptic plasma membrane Mg ATPase activity after 3 weeks administration and mitochondrial Mg ATPase activity after 1 week. There is no effect on synaptic plasma membrane Na-K ATPase activity. Salt supplementation reduced the toxic effects of lithium administration and it is suggested that toxicity may account for some of the previously reported changes in synaptic membrane ATPases produced by lithium. 39 references. (Author abstract)

002039 Hesketh, J. E.; Nicolaou, N. M.; Arbuthnott, G. W.; Wright, A. K. Centre de Neurochimie, 11 rue Humann, Strasbourg, France **The effect of chronic lithium administration on dopamine metabolism in rat striatum.** Psychopharmacology (Berlin). 56(2):163-166, 1978.

The effect of chronic lithuim chloride on striatal dopamine and its metabolites was studied in rats. Results showed an increase in homovanillic acid and 3,4-dihydroxyphenylacetic acid levels but no significant change in dopamine concentration after 3 weeks of lithium administration. There was no change in tyrosine hydroxylase activity after 1, 2, and 3 weeks treatment. The results indicate an increase in the release and turnover of dopamine in the lithium treated animals. 23 references. (Author abstract modified)

002040 Hiller, Jacob M.; Simon, Eric J.; Crain, Stanley M.; Peterson, Edith R. Department of Medicine, New York University School of Medicine, New York, NY 10016 **Opiate receptors in cultures of fetal mouse dorsal root ganglia (DRG) and spinal cord: predominance in DRG neurites.** Brain Research (Amsterdam). 145(2):396-400, 1978.

To examine the development of opiate receptors, stereospecific opiate binding was measured in clusters of isolated dorsal root ganglia (DRG) and spinal cord cross-sections with and without attached DRGs from 14-day-old fetal mice. Explants were incubated in diprenorphine with and without levallorphan. Results show the existence of high levels of opiate receptors located primarily in the neuritic outgrowth from the sensory DRG neurons. The central branches of the DRG neurites in these organotypic cord/ganglion cultures form functional afferent synaptic networks with dorsal horn neurons. Presence of high levels of opiate receptors in the neuritic outgrowths suggests location of opiate receptors on the presynaptic afferent fibers in the spinal cord. It is suggested that DRG and spinal cord cultures may prove useful model systems for developmental studies of opiate receptors and probably also of endorphins. 21 references.

002041 Hinzen, D. H.; Davies, Margaret A. Institute for Normal and Pathological Physiology, University of Cologne, D-5000 Cologne 41, Germany **Synaptic connexions and related postsynaptic pharmacology studied in the cerebral ganglion of Aplysia.** Brain Research (Amsterdam). 144(1):49-62, 1978.

A series of pharmacological studies was undertaken to establish the monosynapticity of interneuronal connections, as well as possible transmitters, of the cerebral ganglion of Aplysia californica, particularly those pathways between two cell groups lcoated on the dorsal surface near the cerebropleural connectives. Monosynapticity was established by the strict one-to-one correlation between presynaptic action potential and excitatory postsynaptic response (EPSP), the constant latency for any given cell pair, gradual change in the EPSP following tetraethylammonium injection into the presynaptic neurone, sustained EPSP in the presence of a high external calcium ion concentration, and sensitivity of the EPSP amplitude to presynaptic polarization. Iontophoretic application of acetylcholine, 5-hydroxytryptamine and glutamate on the postsynaptic cells elicited excitatory responses in many cases. Inhibitory responses were obtained by local iontophoresis of dopamine, gamma-aminobutyric acid and occasionally also by acetylcholine. The only agent found to block the EPSP was bufotenine, which also readily blocked the 5-hydroxytryptamine response. Data all point to 5-hydroxytryptamine as a transmitter in the studied synaptic connexions, but it is emphasized that in the absence of biochemical and histological evidence, the role of 5-hydroxytryptamine cannot be regarded as conclusive. 27 references. (Author abstract modified)

002042 Honecker, H.; Hill, R. Institute of Neuropsychopharmacology, Free University Berlin, Ulmenallee 30, D-1000 Berlin 19, Germany **Does long term treatment with amitriptyline alter the monoamine oxidase of rat brain?** Pharmakopsychiatrie/Neuro-Psychopharmakologie (Stuttgart). 10(1):32-35, 1977.

Based on the hypothesis that depression is due to a deficiency in the absolute or relative concentrations of certain biogenic amines, a study was made of the effects of long-term amitriptyline treatment on brain monoamine oxidase (MAO) in vitro and in vivo in female Wistar rats. The animals were given amitriptyline i.p. for 1, 2, or 3 wk. They were decapitated 16 hr after the last injection, and brains were removed, homogenized, and centrifuged to isolate MAO. MAO was measured on the substrates tyramine, tryptamine, and beta-phenylethylamine. MAO activity was unaffected by the amitriptyline, and the Michaelis constants and IC-50 by tranylcypromine were also unaffected. In the in vitro experiments, amitriptyline was added in a concentration of 1 or 10 micromoles. The higher concentration of amitriptyline inhibited deamination of tyramine, tryptamine, and beta-phenylethylamine by 16%, 8%, and 40%, respectively. At amitriptyline concentrations of 1mcM, deamination of tyramine and tryptamine was unaffected. 20 references.

002043 Horrobin, D. F.; Manku, M. S.; Mtabaji, J. P. Univ. de Montreal, Montreal, Canada **A new mechanism of tricyclic antidepressant action. Blockade of prostaglandin-dependent calcium movements.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):19-23, 1977.

The hypothesis that clomipramine may act as a prostaglandin antagonist was tested in perfusion studies of the rat superior mesenteric vascular bed, where potassium and vasopressin cause vasoconstriction by promoting calcium entry from the extracellular fluid, while noradrenaline and angiotensin act by causing calcium release from intracellular stores. It was found that clomipramine inhibited both processes, possibly by selective inhibition of prostaglandin E2 activity. The clomipramine concentrations required lie within the therapeutic range, and it is postulated that some prostaglandin dependent processes in brain may be affected by clomipramine. 9 references. (Author abstract modified)

002044 Hsu, Louise L; Paul, Steven M.; Halaris, Angelos E.; Freedman, Daniel X. Department of Psychiatry, University of Chicago, 950 East 59th Street, Chicago, IL 60637 **Rat brain aryl acylamidase: multiple forms and inhibition effects of LSD, serotonin and related compounds.** Life Sciences (Oxford). 20(5):857-865, 1977.

Inhibitory effects of biogenic amines and of several drugs, including psychotomimetics, on the enzyme activity of two forms of rat brain aryl acylamidase (AAA) were studied. Adult male Sprague-Dawley rats were used as the enzyme source. Through Bio-Gel column chromatography, aryl acylamidase was separated into aryl acylamidase-1 and aryl acylamidase-2. Aryl acylamidase-1 activity was most potently inhibited by d-LSD and 2-Br-LSD, moderately inhibited by serotonin, slightly inhibited by tryptamine, and not affected by l-LSD. Aryl acylamidase-2 was moderately inhibited by d-LSD and 2-Br-LSD, and was unaffected by l-LSD, serotonin, and tryptamine. Bufotenine, 5-methoxytryptamine, N,N-dimethyltryptamine, dopamine, norepinephrine, d-amphetamine, mescaline, histamine, cyclic AMP, and quipazine had no effect on either aryl acylamidase. Kinetic studies with aryl acylamidase-1 indicated competitive inhibition by d-LSD. 18 references.

002045 Ishitani, Ryoichi; Iwamoto, Takio. Dept. of Pharmacology, Faculty of Pharmaceutical Sciences, Josai University, Sakado, Saitama 350-02, Japan **Studies on the subsynaptosomal distribution of psychotropic drugs in rat cerebral cortex.** Japanese Journal of Pharmacology (Kyoto). 27(6):755-762, 1977.

After administration of (3H)imipramine, (3H)dimetacrine and (S35)chlorpromazine by the direct lateral intraventricular injection, synaptosomes rich fraction (FB) was isolated from rat cerebral cortex by differential and three stepwise density gradient centrifugation. The isolated FB fraction was treated by hyposmotic lysis followed by freezing and thawing once or 15 times and fractionated into the subsynaptosomal fractions by five stepwise density gradient centrifugation. The subsynaptosomal distribution of these drugs showed the same distribution patterns; i.e. the larger portion of radioactivity was recovered in the synaptic ghost membranes rich fractions. On the other hand, synaptic vesicles rich fractions contained less radioactivity. On the disrupting process of FB fraction, when the FB fraction was treated by hyposmotic lysis followed by freezing and thawing 15 times, only pellet (FD6) fraction was obtained as compared with freezing and thawing once (four interphase layers were obtained). Morphological examination revealed that the synaptic ghost membranes were located in the FD6 fraction, but morphological damages were not observed. Under these conditions, (3H)imipramine showed a 74.1% of release from the synaptosomes, while release with (3H)dimetacrine and (S35)chlorpromazine was 3.9and 11.3%, respectively. 25 references. (Author abstract)

002046 Ito, Tsugutaka; Hori, Misako; Yoshida, Kouichi; Shimizu, Masanao. Research Lab., Dainippon Pharmaceutical Co., Ltd., Suita, Osaka 564, Japan **Effect of anticonvulsants on thalamic afterdischarge in rats and cats.** Japanese Journal of Pharmacology (Kyoto). 27(6):823-831, 1977.

Effects of anticonvulsants were determined on thalamic afterdischarge in gallamine immobilized cats and d-tubocurarine immobilized rats in order to clarify the participation of anticonvulsants in the thalamus. Thalamic afterdischarge was induced by electrical stimulation of cat nucleus centralis lateralis and rat nucleus reticularis at 50Hz, 1 msec for 4 sec. In cats, diphenylhydantoin, carbamazepine, phenobarbital, and diazepam raised afterdischarge threshold, and shortened its duration induced at twice the threshold voltage. Trimethadione and dipropylacetate raised the threshold, but did not change the duration. In rats, diphenylhydantoin, phenobarbital, and diazepam raised the threshold, and shortened the duration with comparable dose ranges used for cats. Dipropylacetate and acetazolamide raised the threshold, although did not change the duration except for shortening action with a higher dose of dipropylacetate. Trimethadione was without effect. These results suggest that the depressive effect of anticonvulsants on the thalamus is, at least in part, associated with control of the epilepsies. 21 references. (Author abstract)

002047 Iwangoff, P.; Enz, A.; Meier-Ruge, W. Basic Medical Research, Sandoz Ltd., CH-4002 Basel, Switzerland **Incorporation, after single and repeated application of radioactive labelled DH-ergot alkaloids in different organs of the cat, with special reference to the brain.** Gerontology (Basel). 24(Supplement 1):126-138, 1978.

In a paper presented at a workshop on advances in experimental pharmacology of hydergine in Basel, December 1976, a report on a study of the mechanism of time dependent changes of the tissue DH-ergot alkaloid levels in the central nervous system (CNS) and other organs is given. One hour after in-

travenous administration, 3H-DH-ergot alkaloids showed maximal uptake various visceral organs, and in most parts of the CNS of the cat. The clearance function in both groups of tissues was logarithmical linear, the slope of the straight line for the parts of the CNS being considerably flatter. Repeated administration of these drugs demonstrated a higher retention in the CNS than in the other organs. The single dose level in the CNS is reinforced and, in contrast to liver and lung, maintained for at least 24 h. 18 references. (Author abstract modified)

002048 Iwatsubo, Katsuya. Dept. of Pharmacology, Osaka University Dental School, Kita-ku, Osaka 530, Japan **Effect of morphine on dopamine-sensitive adenylate cyclase activity of nucleus accumbens.** Japanese Journal of Pharmacology (Kyoto). 27(6):903-905, 1977.

A study which demonstrates that both acute and chronic administration of morphine produces an enhancement of the activity of dopamine sensitive adenylate cyclase of the rat nucleus accumbens, one of the areas of the mesolimbic system, is presented. An acute dose of morphine produced a 27% increase in basal adenylate cyclase activity and a 41% increase in dopamine sensitive adenylate cyclase activity. Repeated administration of morphine had no effect on basal adenylate cyclase activity, but did produce a 60% increase in dopamine sensitive adenylate cyclase activity. Thus, morphine given either in vitro or in vivo produced the same action on the dopamine receptor in the nucleus accumbens as in the caudate nucleus. 12 references.

002049 Jacobs, John J. Louisiana State University Medical Center, Department of Anatomy, 1542 Tulane Avenue, New Orleans, LA 70112 **Effect of lithium chloride on adrenocortical function in the rat.** Proceedings of the Society for Experimental Biology and Medicine. 157(2):163-167, 1978.

To examine the effects of oral lithium chloride on adrenocortical function, rats were treated with lithium or NaCl for a 2 week period. Data indicate that while chronic lithium administration did not abolish plasma adrenal steroid level fluctuations, it consistently elevated early morning resting plasma corticosterone levels compared to controls. Plasma corticosterone levels were increased 2 hours after a single lithium injection. Further, injection of dexamethasone, an inhibitor of corticotropin release, blocked the lithium stimulated adrenal response in chronically treated rats. Results suggest that lithium results in modulation of the brain/pituitary unit to increase corticotropin release. 24 references.

002050 Johansson, Barbro B. Department of Neurology, University of Goteborg, Goteborg, Sweden **The cerebrovascular permeability to protein after bicuculline and amphetamine administration in spontaneously hypertensive rats.** Acta Neurologica Scandinavica (Kobenhavn). 56(5):397-404, 1977.

The degree of cerebrovascular permeability to protein was compared in normotensive rats (NR) and spontaneously hypertensive rats (SHR) after administration of bicuculline and amphetamine in order to investigate the mechanical cause of blood brain barrier (BBB) dysfunction after an elevation in blood pressure. The degree of protein leakage in the brain was assessed in SHR and NR after the injection of the two blood pressure elevating drugs by visual estimation of protein (dyed with Evans blue) extravasation in brain sections and by routine gamma scintillation counting. EEG recordings and epileptic activity were observed before sacrificing. Bicuculline-induced epileptic activity and amphetamine intoxication werto to give rise to extensive protein leakage in the brain of NR's, but onl mild protein leakage in SHR's. It is suggested that the SHR's lack normal compensatory vasodilation in response to increased blood pressure; and that this is probably due to decreased lumen to wall ratio in the cerebral arterioles. 19 references.

002051 Johnson, Kenneth M.; Dewey, William L.; Ritter, Katherine S.; Beckner, Jacqueline S. Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX 77550 **Cannabinoid effects on plasma corticosterone and uptake of 3H-corticosterone by mouse brain.** European Journal of Pharmacology (Amsterdam). 47(3):303-310, 1978.

The effects of three cannabinoids, 11-hydroxy-delta9-tetrahydrocannabinol (11-OH-delta9-THC), delta9-THC and cannabinol (CBN), ranging in behavioral activity from high to low, were studied on two aspects of pituitary/adrenal function in mice. Plasma corticosterone levels were used as an index of adrenocorticotropic hormone (ACTH) release. All three cannabinoids elicited an increase in plasma corticosterone levels in a manner similar to their behavioral potency. These cannabinoids also elicited an increase in the concentration of (3H)corticosterone taken up by the brains of adrenalectomized mice in a manner similar to their potency in elevating plasma corticosterone levels. The significance and possible underlying mechanism of the apparent correlation resulting between these effects and the behavioral effects of cannabinoids are discussed. 36 references. (Author abstract)

002052 Johnson, Stephen M.; Westfall, David P.; Howard, Stephen A.; Fleming, William W. Dept. of Pharmacology, West Virginia Univ. Medical Center, Morgantown, WV 26506 **Sensitivities of the isolated ileal longitudinal smooth muscle-myenteric plexus and hypogastric nerve-vas deferens of the guinea pig after chronic morphine pellet implantation.** Journal of Pharmacology and Experimental Therapeutics. 204(1):54-66, 1978.

In a study of sensitivities of the isolated ileal longitudinal smooth muscle/myenteric plexus and hypogastric nerve/vas deferens of the guinea-pig after chronic morphine pellet implantation, tolerance was indicated by 4.5fold subsensitivity to the inhibitory effects of morphine on electrically-induced twitch responses of the longitudinal smooth muscle myenteric plexus preparation of the ileum. Tolerance to morphine was accompanied by supersensitivity to the contractile effects of 5-hydroxytryptamine (5-HT), nicotine and KCl. Sensitivity to acetylcholine was not significantly altered by morphine implantation. Tetrodotoxin or atropine antagonized responses to KCl to a greater extent in morphine tolerant than in control tissues, so that in the presence of either of these agents, the sensitivities of tolerant and control tissues did not differ significantly. These findings suggest that the contractile response to KCl is mediated in part by an excitatory effect on neural elements in the myenteric plexus and that this effect is enhanced in morphine tolerant tissues. Treatment with 5-HT for 60 to 90 minutes eliminated contractile responses to 5-HT but did not alter the magnitude of supersensitivity to KCl, which was therefore not mediated by release of 5-HT from the plexus. Nonspecific supersensitivity (to 5-HT, nicotine and KCl) may reflect compensatory partial depolarization of cholinergic neurons, rather than changes in receptors, after prolonged inhibition by morphine in vivo. In the guinea-pig vas deferens, which does not possess opiate receptors, responses to transmural or preganglionic nerve stimulation, or to KCl, were not altered after morphine pellet implantation. The results suggest that the occurrence of supersensitivity in tis-

sues from animals treated chronically with morphine may be related to the presence of opiate receptors and the development of tolerance to morphine. 40 references. (Author abstract modified)

002053 Juhasz, Laszlo; Dairman, Wallace. Department of Toxicology, Hoffmann-La Roche, Nutley, NJ 07110 **Effect of sub-acute diazepam administration in mice on the subsequent ability of diazepam to protect against metrazol and bicuculline-induced convulsions.** Federation Proceedings. 36(3):377, 1977.

Paper presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977, reports the effects of subacute administration of diazepam on its ability to protect against clonic convulsions induced by metrazol and bicuculline in male CD-1 mice. Mice were given diazepam or vehicle orally for 4 days. On the 5th day, they were given a graded dose of diazepam followed 1 hr later by metrazol or bicuculline i.v. The antimetrazol activity of diazepam was similar in the acute and subacute groups, but the antibicuculline activity differed widely in the two groups, with the diazepam dosage preventing convulsions in the subacute group being 31% of that in the acute group. Since bicuculline is a GABA receptor blocker, it is postulated that the GABA releasing properties of the benzodiazepine derivatives are related to the sedative or ataxic effects and not to the antianxiety effect. 2 references. (Journal abstract modified)

002054 Kantak, K. M.; Wayner, M. J.; Tilson, H. A.; Dwoskin, L. P.; Stein, J. M. Brain Research Laboratory, Syracuse University, 601 University Avenue, Syracuse, NY 13210 **Synthesis and turnover of 3H-5-hydroxytryptamine in the lateral cerebroventricle.** Pharmacology Biochemistry and Behavior. 8(2):153-161, 1978.

The lateral cerebroventricle was perfused using two different labeling procedures in three separate experiments on 5-hydroxytryptamine metabolism and the sensitivity of 5-hydroxytryptamine metabolism to various drugs was subsequently determined. It was demonstrated that two serotonin reuptake blockers, imipramine and fluoxetine, increase the efflux of (3H)5-hydroxytryptamine into the ventricle without affecting the efflux of (3H)5-hydroxyindoleacetic acid while BL-3912A, a drug with weak serotonin agonist activity, also increased the efflux of 3H-5-hydroxytryptamine into the ventricle. 13 references. (Author abstract)

002055 Kaplan, Bonnie J.; Williamson, Peter D. Neuropsychology Laboratory, 116B1, VA Hospital, West Haven, CT 06516 **Electroencephalogram and somatosensory evoked potential changes after administration of six convulsant drugs.** Experimental Neurology. 59(1):124-136, 1978.

To determine whether previously reported electrophysiological changes associated with the effects of convulsant drugs in mammalian brain are indicative of general increases in neuronal excitability or whether they vary as a function of the different modes of convulsant action, cats with chronically implanted electrodes were administered intraperitoneal injections of six convulsant drugs: allyglycine, bemegride, bicuculline, picrotoxin, pentylenetetrazol, and strychnine. The electroencephalogram (EEG) was monitored continuously and somatosensory evoked potentials were elicited during the period to seizure onset. Enhancement of the primary response of the evoked potentials recorded at the cortex paralleled the increases in EEG paroxysmal activity. Both EEG and evoked potential changes were regarded as indicating general preseizure excitability rather than varying with the presumed mechanisms of the individual drugs. 27 references. (Author abstract modified)

002056 Katz, J. B.; Catravas, G. N. Biochemistry Department, Armed Forces Radiobiology Research Institute, Bethesda, MD 20014 **3′,5′-Cyclic guanosine monophosphate levels in rat cerebellum: effects of morphine, ketamine, harmaline and isoniazid.** Federation Proceedings. 36(3):802, 1977.

A study of the effects of morphine, ketamine, harmaline, and isoniazid on cyclic-GMP levels in rat cerebellum was presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Harmaline increased cyclic-GMP. The rise was partly blocked by pretreatment with morphine, but even high doses of morphine failed to block harmaline-induced tremor and did not reduce cyclic-GMP levels below twice control values. Morphine injected 10 min after harmaline reduced cyclic-GMP levels more potently, but some tremor and cyclic-GMP rise persisted with high morphine. Identical results were obtained in rats chronically treated with morphine. Ketamine injected i.p. before and after harmaline reduced harmaline elevated cyclic-GMP levels to 30% of control value and blocked or abolished harmaline-induced tremor. Isoniazid elevated cerebellar cyclic-GMP to 700% of control levels. Phosphodiesterase activities in soluble fractions of cerebellar homogenates were equal in control rats and in rats treated with morphine, harmaline, and isoniazid. Particulate cerebellar guanylate cyclase activities were equal in control and morphine treated rats, but guanylate cyclase activity was increased 30% in rats receiving harmaline or isoniazid. (Journal abstract modified)

002057 Katz, Jonathan B.; Catravas, George N.; Valases, Charles; Wright, Sanford, J., Jr. College of Veterinary Medicine, Washington State University, Pullman, WA **Morphine reduces cerebellar guanosine-3′,5′-cyclic monophosphate content and elevates cerebrospinal fluid guanosine-3′,5′-cyclic monophosphate content in rhesus monkey.** Life Sciences (Oxford). 22(6):467-472, 1978.

The effects of morphine on cerebellar and cerebrospinal fluid cyclic guanosine-3′,5′-monophosphate (cGMP) were studied in the rhesus monkey. It was found that 20mg/kg morphine to awake rhesus monkeys which had been chronically implanted with catheters for aspiration of cerebrospinal fluid produced a significant elevation in the CSF level of cGMP. Additionally, biopsies of cerebral and cerebellar cortex were taken from anesthetized monkeys given 20mg/kg of morphine sulfate. Only cerebellar cGMP levels changed significantly, showing a 35% decrease relative to anesthetized controls. Although the controlling factors of brain tissue and CSF cGMP levels are poorly understood, the possibility of a reciprocal relationship between cGMP levels in certain brain regions and in CSF under some conditions is discussed. 19 references. (Author abstract modified)

002058 Kesner, Raymond P.; Priano, Dee J.; Gold, Timothy. Department of Psychology, University of Utah, Salt Lake City, UT 84112 **Time-dependent disruptive effects of apomorphine and alpha-methyl-p-tyrosine on development of morphine tolerance.** Psychopharmacology (Berlin). 55(2):177-181, 1977.

To examine possible temporal gradients of various pharmacological agents on the disruption of morphine tolerance, apomorphine, haloperidol, propranolol, alpha-methyl-p-tyrosine (AMPT) or diethyldithiocarbonate were administered to rats 5 min, 3 hr, or 12 hr following intraperitoneal administration of morphine. The development of one trial morphine tolerance is disrupted by postadministration of apomorphine at 5 min but not at 3 hr, or by AMPT at 5 min and at 3 hr, but not at 12 hr. Diethyldithiocarbamate, propranolol, and

haloperidol have no disruptive effect. Results suggest that the development of tolerance to the analgesic effects of morphine is mediated by sequential time dependent biochemical processes starting with inhibition of dopaminergic receptors, and followed by an increase in dopamine biosynthesis. 26 references. (Author abstract modified)

002059 Kessler, M.; Hoper, J.; Ji, S. Max-Planck-Institut fur Systemphysiologie, D-4600 Dortmund, Germany **Action of norepinephrine on microcirculation and PO2 distribution in the isolated perfused rat liver.** Gerontology (Basel). 24(Supplement 1):55-65, 1978.

In a paper presented at a workshop on experimental pharmacology of hydergine in Basel, December 1976, a study on the action of norepinephrine on microcirculation and potassium distribution in isolated rat livers is reported. It was found that the addition of a potent vasoconstrictor, such as norepinephrine, induces an influx of sodium and an efflux of calcium and potassium in the parenchymal cells of the perfused liver. This reaction can be reversed by the addition of dihydroergotoxine mesylate. The example shows clearly that very distinct biological signals are generated under such conditions at the membrane level of the hepatocytes and presumably of other cells of liver tissue. It is concluded that present investigations cannot clearly answer the question of whether or not swelling and shrinkage of parenchymal cells and of endothelial cells can serve as an additional mechanism for regulating microcirculation. 32 references. (Author abstract modified)

002060 Kilts, C.; Rech, R. H. Department of Pharmacology, Michigan State University, East Lansing, MI 48824 **Effects of diazepam on dopamine turnover in neostriatal and limbic regions of the rat brain.** Federation Proceedings. 36(3):383, 1977.

A paper presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977, reports a study of effects of diazepam on brain monoamines in the rat, using a dose of diazepam which attenuated the conditioned emotional response in rats without affecting background appetitive responding. Dopamine turnover in the neostriatum, olfactory tubercle, nucleus accumbens, and amygdala was estimated by the rate of dopamine decline following alpha-methyltyrosine i.p. Tissue samples were punched from brain sections 400 micrometers thick. Dopamine levels in all brain areas studied declined exponentially after treatment with alpha-methyltyrosine, and diazepam reduced this rate of dopamine decline. Treatment with diazepam in the absence of alpha-methyltyrosine did not alter dopamine levels. Following delta-butyrolactone i.p. steady state levels of dopamine increased in the neostriatum, olfactory tubercle, and nucleus accumbens, but not in the amygdala. 1 reference. (Journal abstract modified)

002061 Kobayashi, R. M.; Fields, J. Z.; Hruska, R. E.; Beaumont, K.; Yamamura, H. I. VA Hospital, 3350 La Jolla Village Drive, San Diego, CA 92161 **Brain neurotransmitter receptors and chronic antipsychotic drug treatment: a model for tardive dyskinesia.** In: Hanin, I., Animal models in psychiatry and neurology. Elmsford, N. Y., Pergamon Press, 1977. 499 p. (p. 405-409).

In a paper presented at a workshop on animal models in psychiatry and neurology held in Rockville, Maryland, in June 1977, a study of the effects of haloperidol and of clozapine on rat brain dopamine (DA), muscarinic cholinergic, and gamma-aminobutyric acid (GABA) receptors is reported. The study examined the hypothesis that antipsychotic efficacy is directly related to dopamine (DA) receptor blockade, while extrapyramidal side-effects are inversely related to muscarinic cholinergic receptor blockade. Chronic haloperidol treatment (but not acute administration of the drug) significantly increased the number of DA receptor binding sites in the caudate nucleus for up to 7 days after cessation of treatment. By 14 days after cessation of treatment, the number of DA receptor binding sites had returned to control levels. Haloperidol had no effect on DA receptor binding in the hippocampus or on muscarinic receptor binding or in GABA receptor binding. Clozapine, which is associated with a low incidence of tardive dyskinesia, markedly reduced muscarinic receptor binding following acute administration of a 100mg/Kg dose. Acute or chronic treatment with 30mg/Kg clozapine had no effect of muscarinic receptor binding. Clozapine did not alter DA, muscarinic, or GABA receptor binding in the caudate nucleus or hippocampus when measured 1 day or 7 days after cessation of chronic treatment. It is suggested that the chronic haloperidol-induced increase in caudate nucleus DA receptors may provide a suitable laboratory model for tardive dyskinesia. 14 references.

002062 Koffer, Kenneth B.; Berney, Stuart; Hornykiewicz, Oleh. Dept. of Psychopharmacology, Clark Inst. of Psychiatry, Univ. of Toronto, Toronto, Ontario M5T 1R8, Canada **The role of the corpus striatum in neuroleptic- and narcotic-induced catalepsy.** European Journal of Pharmacology (Amsterdam). 47(1):81-86, 1978.

The role of the corpus striatum in neuroleptic and narcotic-induced catalepsy was examined in the rat. Bilateral lesions of the corpus stratium were observed to attenuate chlorpromazine-induce catalepsy. However, analogous lesions of the corpus striatum potentiated morphine-induced catalepsy. These results suggest that: 1) the corpus striatum may be the primary site of action of neuroleptic drugs in the production of catalepsy; and 2) narcotic (morphine) induced catalepsy may not be exclusively mediated by the corpus striatum. 25 references. (Author abstract modified)

002063 Kovacevic, R.; Kaminski, M.; Radulovacki, M. Department of Pharmacology, University of Illinois Medical Center, Chicago, IL 60680 **Effects of diethyldithiocarbamate on brain monoamine and protein content in neonatal rats.** Federation Proceedings. 36(3):353, 1977.

Effects of diethyldithiocarbamate (DDC), an inhibitor of dopamine-beta-hydroxylase and a norepinephrine depleter, on brain monoamine and protein content in 7 day Sprague-Dawley rats will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Rats received DDC s.c. or saline daily for 7 days and were decapitated 24 hr after the last injection. Whole brains were analyzed for norepinephrine, dopamine, homovanillic acid, serotonin, 5-hydroxyindoleacetic acid, and total protein content. DDC produced a significant decrease in norepinephrine and total brain protein content, while no changes occurred in the other metabolites, except for a slight dopamine elevation. Brainweight and bodyweight were significantly decreased. The simultaneous reduction in norepinephrine and brain protein by DDC is of interest because norepinephrine depletion has been reported to cause deprivation of paradoxical sleep, while increased protein synthesis has been associated with paradoxical sleep. (Journal abstract modified)

002064 Kuczenski, Ronald Dept. of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN 37232 **Biphasic**

effects of amphetamine on striatal dopamine dynamics. European Journal of Pharmacology (Amsterdam). 46(3):249-257, 1977.

The effects of amphetamine (AMPH), over wide ranges of dose and time parameters, on the conversion of radiolabeled tyrosine to dopamine (DA) in vivo and on the levels of endogenous DA in rat striatum were investigated. DA formation exhibited a biphasic dose response to AMPH. At 16 minutes and 31 minutes after AMPH administration, DA accumulation increased linearly to a maximal rate of 200% of control values at 1mg/kg, then declined to less than 50% of control values of AMPH doses of 5mg/kg or more. As a function of time, low doses of AMPH only increased DA accumulation, whereas high doses only decreased DA accumulation. All doses of AMPH increased endogenous levels of striatal DA. The data are discussed in terms of compensatory adaptive mechanisms of the nigrostriatal dopaminergic pathway. 44 references. (Author abstract modified)

002065 Kuhn, Cynthia M.; Schanberg, Saul M.; Breese, George R. Dept. of Physiology and Pharmacology, Duke Univ. Medical Center, Durham, NC 27710 **Metabolism of amphetamine by rat brain tissue.** Biochemical Pharmacology (Oxford). 27(3):343-351, 1978.

The metabolism of amphetamine by rat brain tissue was investigated in vivo and in vitro with the use of labelled amphetamine. p-Hydroxyamphetamine (POHA), norephedrine (NOR), and p-hydroxynorephedrine (POHNOR) were assayed in brain tissue after intracisternal administration of amphetamine. Brain content of POHA and NOR declined quickly, while brain POHNOR content rose gradually and then decreased. It was demonstrated that these metabolites had not been formed peripherally. POHA and POHNOR only were decreased by pretreatment of rats with iprindole, and POHNOR and NOR formation was reduced by pretreatment with U14-624. Findings indicated that amphetamine can be metabolized by brain tissue to the hydroxylated metabolites POHA, NOR, and POHNOR, although brain content of these metabolites represents a small fraction of the dose of amphetamine. Data also suggested that POHA is formed outside of catecholamine nerve terminals, while POHNOR and NOR are formed in noradrenergic nerve terminals. 65 references. (Journal abstract modified)

002066 Labrecque, G.; Halle, S.; Berthiaume, A.; Morin, G.; Morin, P. J. Departement de Pharmacologie, Universite Laval, Ste-Foy, Quebec G1K 7P4, Canada **Potentiation of the epileptogenic effect of penicillin G by marihuana smoking.** Canadian Journal of Physiology and Pharmacology (Ottawa). 56(1):87-96, 1978.

The effects of subconvulsive doses of penicillin after acute or chronic marihuana smoking were investigated. Twenty-four mongrel dogs received 4mg/kg morphine per kilogram, intramuscularly, and 750 000 IU sodium penicillin G per kilogram, intravenously. In acute experiments, the animals smoked eight cigarettes containing approximately 6mg of delta9-tetrahydrocannabinol. In chronic experiments, they smoked four cigarettes per day for 10 weeks before being studied. Ten animals (five controls and five acute smokers) were observed visually while the electrocorticogram (ECoG) was recorded in the 14 others (five controls, five acute, four chronic). This last group received 20 to 30mg succinylcholine chloride as muscle relaxant. Penicillin had no effect either on the behavior or on the ECoG in nine of the ten controls. Nine out of the ten acute smokers showed coarse tremors of the limbs and epileptiform waves. Two of the four chronic smokers had typical epileptiform episodes. The results suggest that marihuana smoking produces a blood-brain barrier permeability change towards sodium penicillin G. Another explanation could be that Cannabis modifies the excitability threshold of the brain. 30 references. (Author abstract modified)

002067 Laduron, Pierre M.; Janssen, P. F. M.; Leysen, Josee E. Dept. of Biochemical Pharmacology, Janssen Pharmaceutica, B-2340 Beerse, Belgium **Spiperone: a ligand of choice for neuroleptic receptors: 3. subcellular distribution of neuroleptic drugs and their receptors in various rat brain areas.** Biochemical Pharmacology (Oxford). 27(3):323-328, 1978.

Tissue fractionation was used as an analytical tool to study, in various rat brain regions, the subcellular distribution of the neuroleptic receptor and labeled neuroleptics previously injected into the animals. Distribution patterns of various marker enzymes were also determined to assess the composition of different subcellular fractions. After homogenate centrifugation, labeled spiperone binding receptors together with 5'-nucleotidase were found to be mainly enriched in the microsomal fraction. Similarly, after injection of labeled spiperone or pimozide into rats, radioactivity was recovered in the microsomal fraction in the striatum, the olfactory tubercle and nucleus accumbens, and the frontal cortex, but not the cerebellum. After equilibration, the distribution pattern of spiperone revealed a mean peak in a gradient region of low density close to that of 5'-nucleotidase. The results indicate that receptor sites of neuroleptic drugs in the brain dopaminergic areas are associated with membrane-like structures but not with mitochondria or nerve terminals containing dopamine. 16 references. (Journal abstract modified)

002068 Laduron, Pierre M.; Janssen, P. F. M.; Leysen, Josee E. Dept. of Biochemical Pharmacology, Janssen Pharmaceutica, B-2340 Beerse, Belgium **Spiperone: a ligand of choice for neuroleptic receptors. 2. Regional distribution and in vivo displacement of neuroleptic drugs.** Biochemical Pharmacology (Oxford). 27(3):317-321, 1978.

Specific in vitro and in vivo binding of neuroleptic drugs was demonstrated by studying the regional distribution in rat brain. Labelled spiperone and pimozide were found to be specifically taken up in the dopaminergic areas of the brain, a fact correlating with distribution of neuroleptic receptors when measured under in vitro conditions. Larger doses of unlabeled neuroleptics only displaced the labeled neuroleptic in vivo in the dopaminergic areas (striatum, nucleus accumbens, tuberculum olfactorium, and frontal cortex) but not in the cerebellum. Dopamine agonists were found to partly displace the labeled spiperone in the striatum, providing further evidence about the dopaminergic nature of the neuroleptic receptor. Some in vivo experiments have suggested that the neuroleptic receptor is not the same in all the dopaminergic areas. It was concluded that spiperone is a ligand of choice for in vivo studies of neuroleptic receptors. 16 references. (Journal abstract modified)

002069 Laihinen, A.; Valleala, P. no address **The relationship between cortical recruiting responses and ponto-geniculo-occipital (PGO) waves during paradoxical sleep and after the administration of reserpine in the cat.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):460-461, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, the relationship between cortical recruiting responses and pontogeniculooccipital (PGO) waves during paradoxical sleep and after the administration of reser-

pine in the cat is discussed. It was observed that during paradoxical sleep in cats in which the nucleus centrum medianum of the thalamus was being stimulated at a frequency of 9c/s, PGO waves (PGOps) in the geniculate nuclei did not occur in the presence of recruiting responses recorded from the motor cortex. This effect was most pronounced with respect to series of PGO waves which usually occur at a frequency of 4 to 7c/s. The same effect was shown by PGO waves (PGORES) in reserpinized cats which were given Serpasil (reserpine). On the basis of these experiments it was concluded that PGO waves and recruiting responses are reciprocal events and at least to a certain extent mutually exclusive. This negative association may reflect the fact that the occurrence of PGO waves not only heralds but also parallels the desynchronizing tendency whereas recruiting responses reflect the synchronizing mechanism. These results confirm the hypothesis that PGOPS and PGORES are related phenomena, having some components in common in spite of the different experimental conditions. (Author abstract modified)

002070 Lalonde, Josee; Normand, Maurice. Lab. d'Endocrinologie-Biocontroles, Departement de Physiologie, Faculte de Medicine, Universite Laval, Quebec, Quebec G1K 7P4, Canada **Metabolic clearance rate of adrenocorticotropin in the rat.** Canadian Journal of Physiology and Pharmacology (Ottawa). 55(5):1079-1083, 1977.

Rats were pretreated with chlorpromazine, morphine, and pentobarbital to block endogenous adrenocorticotropin (ACTH) release so that the metabolic clearance rate of ACTH could be examined after the intravenous infusion of graded rates of the hormone. The metabolic clearance rate of ACTH decreased as infusion rates increased. Previous studies have shown that the metabolic clearance rate of corticosterone increases as a function of the infusion rate of the steroid. It is posited that the metabolism of these two hormonal links of the hypothalamo/pituitary/adrenocortical axis vary in opposite fashions as a function of the secretion rate of the hormone. 24 references. (Author abstract modified)

002071 Laska, Frank J.; Fennessy, Max R. Dept. of Pharmacology, University of Melbourne, Parkville, Victoria 3052, Australia **Induction of physical dependence on cyclazocine and pentazocine in the rat.** European Journal of Pharmacology (Amsterdam). 48(1):57-65, 1978.

Due to the possible abuse potential of the benzomorphan derivatives cyclazocine and pentazocine, a study was conducted to determine whether slow release emulsions of these compounds could induce physical dependence of the morphine type in the rat. Rats were treated for 24, 48 or 72 h with slow release (SR) emulsions of morphine (75, 100 and 150mg/kg), cyclazocine (75, 100 and 150mg/kg) or pentazocine (100, 200 and 400mg/kg). At these times the degree of physical dependence was assessed by examining the abstinence behavior (jumps and wet shakes) and changes in body temperature and bodyweight induced by naloxone (5mg/kg). The effects of SR treatments on brain levels of noradrenaline (NA), dopamine (DA), homovanillic acid (HVA), 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) were also determined at these times. The results show that all three opiates induce physical dependence in the order of severity of morphine greater than cyclazocine greater than pentazocine. An elevation of 5-HT turnover also appears to be associated with the dependence produced by these opiates. These findings indicate that the increase in brain 5-HT metabolism is not a primary causative factor during opiate dependence, but occurs in response to some other process. 26 references. (Author abstract modified)

002072 Lee, R. L.; Spencer, P. S. J. Applied Pharmacology Laboratories, Welsh School of Pharmacy, UWIST, Cardiff, Wales **The effect of clomipramine and other amine-uptake inhibitors on morphine analgesia in laboratory animals.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):53-61, 1977.

The effect of clomipramine and other amine uptake inhibitors on morphine analgesia in laboratory animals was examined. Repeated dose studies with morphine showed that combination with clomipramine induced more severe tolerance more rapidly, whereas maprotiline delayed and alleviated morphine tolerance. It is postulated that any drug which enhances the short-term effects of morphine will also enhance the speed of onset and severity of tolerance. For long-term therapy therefore it is suggested that morphine may be better combined with maprotiline. 27 references. (Author abstract modified)

002073 Lefkowitz, Stanley S.; Klager, Karen; Nemeth, Doris; Pruess, Mary. Dept. of Microbiology, Texas Tech University School of Medicine, Lubbock, TX 79409 **Immunosuppression of mice by delta-9-tetrahydrocannabinol.** Research Communications in Chemical Pathology and Pharmacology. 19(1):101-107, 1978.

Studies were initiated to determine the effects of delta-9-tetrahydrocannabinol (THC) on the production of indirect IgG plaque forming and rosette forming cells in mice. BDF1 mice were immunized with sheep erythrocytes followed by multiple injections of 10, 25 or 40mg/kg THC. Results indicated that both parameters were significantly reduced by 25mg/kg, thus affirming the immunosuppressive properties of THC in mice. 12 references. (Author abstract)

002074 Leibowitz, Sarah Fryer. Rockefeller University, New York, NY 10021 **Paraventricular nucleus: a primary site mediating adrenergic stimulation of feeding and drinking.** Pharmacology Biochemistry and Behavior. 8(2):163-175, 1978.

Thirty-five different brain areas in over 500 rats were examined to localize the precise region of norepinephrine (NE) sensitivity. Essentially all sites outside the hypothalamus, as well as in the lateral portion of the hypothalamus, were relatively or totally unresponsive to NE. In the medial hypothalamic area, the paraventricular nucleus (PVN) was clearly distinguished as the most effective site for initiating both feeding and drinking with noradrenergic activiation in the satiated animal. Sites greater than 0.5mm rostral, caudal, dorsal, ventral or lateral to this nucleus yielded significantly smaller effects. In mildly hungry rats, NE was found to potentiate the ongoing feeding response, and anatomical analyses of this phenomenon showed the PVN to be most responsive, with a smaller but reliable potentiation occurring along the periventricular hypothalamus adjacent to the third ventricle. Norepinephrine injected into the lateral perifornical hypothalamic area actually produced a suppression of feeding in these hungry animals. These findings, together with results from other studies, converge on the medial PVN region as being a key link in the process of increased food and water consumption associated with increased noradrenergic activity. 79 references. (Author abstract modified)

002075 Leslie, Steven W.; Elrod, Steve V.; Bonner, Hugh W. Dept. of Pharmacology, College of Pharmacy, University of Texas at Austin, Austin, TX 78712 **Effects of chlorpromazine and dl-amphetamine on calcium uptake by adrenal chromaffin cell membrane.** Biochemical Pharmacology (Oxford). 27(1):114-116, 1978.

The effect of chlorpromazine and racemic amphetamine on calcium (Ca) uptake by bovine adrenal chromaffin cell membrane was investigated in vitro. Chlorpromazine had no effect on the adenosine triphosphate (ATP) dependent radiolabeled Ca uptake process, but, in high concentrations, it depressed nonspecific Ca binding to membranes of the microsomal fraction. Amphetamine increased ATP dependent Ca uptake and potentiated nonspecific Ca membrane binding. Neither drug altered Ca dependent adenosine triphosphatase activity. It is suggested that amphetamine does not act on the ATP dependent Ca pump. 14 references.

002076 Levin, R. M.; Weiss, B. Department of Pharmacology, Medical College of Pennsylvania, Philadelphia, PA 19129 **Binding of antipsychotic agents to the cyclic nucleotide activator.** Federation Proceedings. 36(3):319, 1977.

Action of antipsychotic agents on the cyclic nucleotide system of the brain was discussed at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. These agents inhibit catecholamine sensitive adenylate cyclase and activator sensitive phosphodiesterase. Trifluoperazine binds to purified cyclic nucleotide activiator at two distinct sites: a high affinity, calcium dependent site and a low affinity, calcium independent site. In experimental studies only activator protein displayed high affinity, calcium dependent binding for trifluoperazine, while cytochrome C, chymotrypsinogen, BSA, aldolase, and catalase displayed only low affinity, calcium independent binding. Trifluoperazine binding to activator markedly decreased when pH was raised from 7.5to 8.0, whereas calcium independent binding was not altered by changes in pH between 6.5and 8.5. Pimozide and penfluridol showed a similar calcium specific binding to activator, but chlordiazepoxide did not. This activator modulates both phosphodiesterase and adenylate cyclase; the binding of antipsychotic drugs to this activator explains the inhibition by these drugs of certain forms of phosphodiesterase and adenylate cyclase. (Journal abstract modified)

002077 Levy, Matthew N.; Blattberg, Benjamin. Div. of Investigative Medicine, Mt. Sinai Hospital, 1800 E. 95th St., Cleveland, OH 44106 **The influence of cocaine and desipramine on the cardiac responses to exogenous and endogenous norepinephrine.** European Journal of Pharmacology (Amsterdam). 48(1):37-49, 1978.

The influence of cocaine and desipramine on the cardiac response to exogenous and endogenous norepinephrine (NE) was studied in an attempt to determine whether previous discrepant findings reflect true differences in the drugs' mechanism of action or side-effects or whether they may be attributable to disparities in experimental conditions. It was found that in open chest, anesthetized dogs, cocaine and desipramine potentiated the pressor, chronotropic, inotropic and coronary sinus blood flow responses to norepinephrine (NE) infusions. The chronotropic and inotropic responses were also prolonged, and the extraction of exogenous NE from the coronary blood stream was diminished. Cocaine and desipramine also potentiated the pressor and coronary sinus blood flow responses, but not the chronotropic or inotropic responses, to stimulation of the left ansa subclavia. The inotropic response was slightly prolonged, however, and the chronotropic response was markedly prolonged. The overflow of NE into the coronary sinus blood was not increased by either neuronal uptake blocking agent. It is proposed that cocaine and desipramine, at the doses employed, diminish the release of NE from the cardiac nerve endings at the same time that they inhibit reuptake of the neurotransmitter. Their mechanisms of action and their side effects on the circulatory system do not appear to differ significantly. 41 references. (Author abstract modified)

002078 Lew, J. Y.; Hata, F.; Goldstein, M. Neurochemistry Laboratories, Department of Psychiatry, New York University Medical Center, New York, NY 10016 **Effect of ergot alkaloids and of neuroleptics on binding to putative dopamine and alpha receptors.** Federation Proceedings. 36(3):327, 1977.

Effects of ergot alkaloids on the postsynaptic dopamine receptor and the alpha-receptor will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. The effects of hydergine, 2-bromo-alpha-ergocryptine, and lergotrile on the binding of tritiated dopamine and tritiated haloperidol to bovine striatal membranes was investigated. 2-Bromo-alpha-ergocryptine and lergotrile competed effectively for the specific binding of dopamine and haloperidol. 2-Bromo-alpha-ergocryptine and hydergine were much more potent displacers of haloperidol, while lergotrile was a more potent displacer of dopamine. To determine the effects of ergots and major tranquilizers at the alpha-receptor, the effects of these compounds on the binding of tritiated dihydroergocryptine and tritiated WB-4101 to cortical membranes was studied. All drugs studied were potent displacers of dihydroergocryptine and WB-4101. Lesions in the medial forebrain bundle, which destroyed noradrenergic pathways, increased the specific binding of dihydroergocryptine. (+)-Butaclamol was 150 times more effective than (-)-butaclamol and clozapine was as effective as haloperidol in displacing WB-4101. 1 reference. (Journal abstract modified)

002079 Leysen, Josee E.; Gommeren, W.; Laduron, Pierre M. Dept. of Biochemical Pharmacology, Janssen Pharmaceutics, B-2340 Beerse, Belgium **Spiperone: a ligand of choice for neuroleptic receptors. 1. Kinetics and characteristics of in vitro binding.** Biochemical Pharmacology (Oxford). 27(3):307-316, 1978.

A binding assay for neuroleptic receptors developed with spiperone as the labelled ligand is discussed. In a standard binding experiment using a total particulate cell fraction the binding of labeled ligand in the presence of butaclamol equaled the binding in the absence of nonlabeled drug and amounted to 53 plus or minus 3 pmoles/g tissue for spiperone and to 31 plus or minus 1 pmoles/g tissue for haloperidol. Receptor sites appeared similar to those of haloperidol, but with more sites per gram of tissue and a biphasic receptor ligand dissociation curve. Receptor sites labelled by both ligands are mainly dopaminergic, but also serotonergic with spiperone. As compared with haloperidol, spiperone showed a two times higher ratio of specific versus aspecific binding, a 10 fold greater association constant, and a slower dissociation of the receptor ligand complex. It was concluded that spiperone is a more suitable ligand than haloperidol for studying the neuroleptic receptors. 15 references. (Journal abstract modified)

002080 Liu, Shean-Jang; Evans, David B.; Wang, Richard I. H. Pharmacology Research Lab. 116 E, VA Center, Wood, WI 53193 **Correlation of urinary excretion of methadone metabolites with methadone metabolism and analgesia in the rat.** Journal of Pharmacology and Experimental Therapeutics. 204(1):67-76, 1978.

To investigate the correlation of urinary excretion of methadone metabolites with methadone metabolism and analgesia in the rat, a study was made. Changes in analgesia and in the percentages of total 14C in the liver or urine as water soluble metabolites (14C-WSM) 3 hours after administration of

(14C)methadone were investigated in rats pretreated with drugs previously shown to change in vitro methadone metabolism. Acute administration of diazepam prolonged the duration of methadone analgesia, increased the brain concentration of total 14C (mostly as unchanged methadone) and decreased the percents of total 14C in liver or urine as WSM. Rats pretreated with phenobarbital for 4 days or fed with methadone in drinking water for 2 weeks developed tolerance to the analgesic effect of methadone. This decreased analgesia was associated with a decreased concentration of 14C in the brain and was accompanied by increases in the amounts of 14C-WSM expressed as percentages of total C in liver or urine. Desipramine given 1 hour before a test dose of methadone, partly restored methadone analgesia in chronically methadone fed rats. Methadone fed rats given desipramine before injection of (14C), methadone had a higher concentration of 14C in the brain and had lower percentages of 14C-WSM in the liver and urine compared to methadone fed rats injected with (14C) methadone alone. The changes in the percentage of total 14C in urine as WSM were proportional to the changes of this percentage in liver and to the duration of methadone analgesia in all of the experiments studied. These studies indicate that the analgesic property of methadone can be prolonged or shortened by compounds which inhibit or stimulate, respectively, the biotransformation of methadone. 24 references. (Author abstract)

002081 Lokhandwala, Mustafa F.; Buckley, Joseph P. Dept. of Pharmacology, College of Pharmacy, University of Houston, Houston, TX 77004 **The effect of L-dopa on peripheral sympathetic nerve function: role of presynaptic dopamine receptors.** Journal of Pharmacology and Experimental Therapeutics. 204(2):362-371, 1978.

Possible contribution of presynaptic dopamine receptors towards the impairment of sympathetic nervous transmission observed after treatment with L-dopa was investigated. Intravenous administration of L-dopa (20mg/kg) to pentobarbital anesthetized dogs produced significant inhibition of cardiac acceleration elicited by electrical stimulation of right postganglionic cardiac sympathetic nerve. Increases in blood pressure and heartrate observed during bilateral occlusion were inhibited, while the pressor and positive chronotropic effects were enhanced after L-dopa. These actions of L-dopa were prevented by prior inhibition of dopa decarboxylase with Ro-4-4602, while inhibition of dopamine beta-hydroxylase by FLA-63 did not alter the actions of L-dopa. Dopamine infusion to desipramine treated dogs caused impairment of cardioacceleration which was prevented with prior treatment with pimozide. Pimozide prevented the inhibition action of L-dopa on sympathetic nerve function to the myocardium and on pressor and positive chronotropic effects of bilateral carotid occlusion. However, L-dopa induced enhancement of the pressor and positive chronotropic effects of tyramine was not affected by pimozide. The data support the concept for the existence of inhibitory dopamine receptors on postganglionic sympathetic nerves and provide evidence that these dopamine receptors may be involved in the impairment of peripheral sympathetic nerve function after treatment with L-dopa. 40 references.

002082 Louvel, J.; Pumain, R. no address **Penicillin in the pyramidal tract: ectopic action potential generation.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):563, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, ectopic action potential generation induced by penicillin in the pyramidal tract of rats is described. Unit activity from pyramidal tract neurons in the rat cerebral cortex was recorded by means of extracellular microelectrodes. A spontaneous cortical action potential triggered an electrical stimulation of the pyramidal tract which in turn evoked an antidromic test action potential. In these conditions, both action potentials repeatedly collided. After a micro injection of Na penicillin-G in the pyramidal tract a great number of action potentials occurring in the cortex did not collide with the test action potentials. It is concluded that these spontaneously occurring action potentials must have been antidromic in nature. Hence, very small amounts of penicillin induce the generation of action potentials at an ectopic site. This site must be located on the course, or at the branching points, or at the terminals of pyramidal tract fibers. These results support the hypothesis of a presynaptic mechanism in the generation of the paroxysmal depolarization shifts known to occur in acute epileptogenic foci: the ectopic repetitive action potential generation in afferent or recurrent fibers would lead to a substantial release of transmitter and therefore contribute to the building up of large postsynaptic potentials. Besides, in the same experimental conditions, EEG spikes develop on the cortex in close temporal relationship with the antidromic action potentials. (Author abstract modified)

002083 Mackinnon, A. Malcolm; Sutherland, Eileen; Simon, Francis R. Dept. of Medicine, Flinders Medical Centre, Bedford Park, South Australia 5042, Australia **Qualitative alteration in hepatic microsomal cytochrome P-450 apoproteins associated with bile duct ligation, and the administration of ethinyl estradiol, phenobarbital and 3-methycholanthrene.** Biochemical Pharmacology (Oxford). 27(1):29-35, 1978.

The possibility that different forms of hepatic cytochrome P-450 may be altered in hepatic disorders associated with impaired drug metabolism was investigated in rats. Total hepatic cytochrome P-450 was decreased after bile duct ligation or after administration of ethinylestradiol. Phenobarbital alone increased hepatic cytochrome P-450 content. When administered with ethinylestradiol, phenobarbital prevented the decrease in cytochrome P-450. Microsomal ethylmorphine N-demethylase activities paralleled the drug-induced changes in cytochrome P-450 content but decreased it following bile duct ligation. Four forms of microsomal cytochrome P-450 apoproteins were tentatively identified by their differential responses to phenobarbital, ethinylestradiol, 3-methylcholanthrene, phenobarbital plus ethinylestradiol, and bile duct ligation via polyacrylamide gel electrophoresis. The mechanism of the phenobarbital-induced reversal of the effects of ethinylestradiol on hepatic cytochrome P-450 was determined by the double isotope technique. Phenobarbital increased the relative synthesis rates of P-450 apoproteins in ethinylestradiol treated rats. The studies support the hypothesis that multiple forms of cytochrome P-450 are present in liver microsomal membranes and that alterations in specific apoproteins may be associated with changes in the functional properties of cytochrome P-450. 36 references. (Author abstract modified)

002084 Maggi, A.; Bruno, F.; Cattabeni, F.; Groppetti, A.; Parenti, M.; Racagni, G. Institute of Pharmacology, University of Milan, I-20129 Milan, Italy **Apomorphine-induced inhibition of striatal dopamine release: role of dopaminergic receptors in substantia nigra.** Brain Research (Amsterdam). 145(1):180-184, 1978.

To determine if dopaminergic receptors in the substantia nigra (SN) might be a site of action of apomorphine-induced inhibition of dopamine (DA) in the striatum, a series of experi-

ments was undertaken in male rats. Results show that levels of striatal 3nmethoxytyramine (3-MT) are reduced following intraperitoneal apomorphine. Injection directly into the SN similarly reduces 3-MT. Apomorphine also increases the in vivo 3',5'-cyclic adenosine monophosphate (cAMP) content in both striatum and SN, indicating an activation of dopaminergic receptors in SN. Further, apomorphine remains able to antagonize the increased DA release elicited by lesioning of the crus cerebri. Electrophysiological findings demonstrate that apomorphine has a powerful inhibitory effect on the firing rate of DA neurons when applied directly onto SN DA cell bodies. In addition to providing further evidence for gamma-aminobutyric acid (GABA) mediated inhibition of the dopaminergic nigrostriatal system, results suggest that DA receptors in SN are not located on GABAergic neurons. Moreover, findings suggest that in addition to the postsynaptic neuronal feedback loops or the intraneuronal biochemical processes mediated by postsynaptic/presynaptic receptors, mechanisms in SN may also regulate neurotransmitter release. 31 references.

002085 Malor, Ron; Jackson, David M.; Chesher, Gregory B. Department of Pharmacology, University of Sydney, Sydney, N.S.W. 2006, Australia **Possible central dopaminergic modulation of the rise in plasma concentration of non-esterified fatty acids produced in the mouse by (-)trans-delta9-tetrahydrocannabinol.** Biochemical Pharmacology (Oxford). 27(4):407-413, 1978.

To examine the possibility of central dopaminergic modulation of the rise in plasma concentrations of nonestrified fatty acids (NEFAs) produced by (-)trans-delta9-tetrahydrocannabinol (delta9-THC), 11-0H THC, 8alpha,11-diOH THC, cannabinol (CBN) and cannabidiol (CBD) were examined for direct lipolytic activity on mouse adipocytes in vitro. None of the cannabinoids showed any marked stimulation of lipolysis, nor did they modify the response of the adipocytes to either isoprenaline or adrenocorticotrophic hormone. In vivo, THC (but not CBN or CBD) produced in mice a dose dependent rise in plasma NEFA. This response was prevented by prior bilateral adrenalectomy or by pretreatment with alpha-methyl-p-tyrosine. Pretreatment with FLA-63 or phentolamine did not alter the lipolytic response to THC. However, the THC-induced rise in plasma NEFA was blocked by prior administration of the dopamine receptor antagonists perphenazine or pimozide. It is suggested that the elevation of plasma NEFA produced in mice by THC is centrally mediated and requires the presence of functional dopaminergic receptors. 27 references. (Author abstract modified)

002086 Manen, Carol-Ann; Costa, Max; Sipes, I. Glenn; Russell, Diane Haddock. University of Arizona Health Sciences Center, Dept. of Pharmacology, Tucson, AZ 85724 **Further evidence of cyclic AMP-mediated hypertrophy as a prerequisite of drug-specific enzyme induction.** Biochemical Pharmacology (Oxford). 27(2):219-224, 1978.

To test the hypothesis that the sequence consisting of the administration of phenobarbital, 3-methylcholanthrene, or the polychlorinated biphenyl, Aroclor 1254, to mice and the resultant early and sequential increase in the acitivities of hepatic cAMP dependent protein kinase(s), ornithine decarboxylase and RNA polymerase I, is involved in both liver hypertrophy and the induction of microsomal mixed function oxygenases, the exhibition of these cAMP mediated events in mice unable to induce aryl hydrocarbon hydroxylase in response to 3-methylcholanthrene was investigated. A single dose of 3-methylcholanthrene was administered to male C57B1/6J (aryl hydrocarbon responsive) and DBA/2J (aryl hydrocarbon nonresponsive) mice. In the C57B1/6J mice, the hepatic cAMP concentration increased to 165% of control within 1 hr. Maximal increases in the activities of liver cAMP dependent protein kinase(s)(160%), ornithine decarboxylase (210%) and RNA polymerase I (120%) occurred at 2 hr, 4 hr, and 6 hr, respectively, in the responsive mice. There were no detectable increases in any of these parameters in the nonresponsive (DBA/2J) mice. Multiple doses of 3-methylcholanthrene resulted in increases in hepatic aryl hydrocarbon hydroxylase (460%) and liver weight/bodyweight ratios (118%) in the responsive (C57B1/6J) mice killed at 5 days. There was no increase in either of these parameters in the nonresponsive (DBA/2J) mice. Both the responsive and nonresponsive mice responded similarly to a single parental dose of phenobarbital with maximal increases in the activities of cAMP dependent protein kinase(s) (150%), ornithine decarboxylase (160%) and RNA polymerase I (135%) at 2 hr, 4 hr, and 8 hr, respectively. Multiple doses of phenobarbital resulted in increased ethylmorphine N-demethylase activity (160%) and liver weight/bodyweight ratios (130%) in both strains of mice at 5 days. These data provide further evidence of coupled cAMP mediated hypertrophy and induction of mixed function oxygenases in liver. 36 references. (Author abstract modified)

002087 Mantione, C. R.; Righter, R. C.; Ellis, D. B. Department of Biochemistry, Hoechst-Roussel Pharmaceuticals, Inc., Somerville, NJ 08876 **Effects of substituted spiro(isobenzofuran-piperidines) on synaptosomal biogenic amine transport.** Federation Proceedings. 36(3):385, 1977.

A paper presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977, reports an investigation of several halogenated analogs of the antidepressant HP-505 (1,3-dihydro-3-phenylspiro-(isobenzofuran-1,4'-piperidine)), for in vitro effect on the uptake of norepinephrine, serotonin, and dopamine in rat brain synaptosomes. These analogs have both neuroleptic and antidepressant activity. They were found to be equipotent or superior to desipramine, nomifensine, and HP-505 in inhibiting norepinephrine uptake, more potent than chlorimipramine in inhibiting serotonin uptake, and more active than benztropine in inhibiting the uptake of dopamine in the striatum. 1 reference. (Journal abstract modified)

002088 Markstein, R.; Wagner, H. Medical and Biological Research Division, Sandoz Ltd., CH-4002, Basel, Switzerland **Effect of dihydroergotoxine on cyclic-AMP-generating systems in rat cerebral cortex slices.** Gerontology (Basel). 24(Supplement 1):94-105, 1978.

In a paper presented at a workshop on advances in experimental pharmacology of hydergine in Basel, December 1976, a study on the effect of dihydroergotoxine (DHET) on cyclic adenosine monophosphate (AMP) generating systems in rat cerebral cortex slices is described. In slices of rat cerebral cortex, cyclic-AMP formation found to be stimulated in response to added noradrenaline (NA), isoproterenol (ISP) or adenosine. The effect of ISP could be antagonized only by the selective beta-adrenoceptor blocking agent pindolol, whereas the stimulating effect of NA could be antagonized by both alpha and beta-adrenoceptor blocking agents. DHET at low concentrations antagonized the stimulating effect of NA but not of ISP or adenosine, suggesting that this substance has a high affinity for central alpha-adrenoceptors. It was also found that DHET is accumulated in rat cerebral cortex after repeated oral applications. In slices of cortex obtained from rats after treatment with DHET for 3 and 6 weeks, but not after 1 week, NA had

a significant lower effect on cyclic-AMP formation than in slices from corresponding controls. 14 references. (Author abstract modified)

002089 Marotta, Rocco Francis. CUNY, New York, NY **Pharmacological manipulations of the septal irritability syndrome: role of dopaminergic mechanisms in recovery of function. (Ph.D. dissertation).** Dissertation Abstracts International. Ann Arbor, MI, Univ. M-films, No.77-20489 HC$15.00 MF$8.50 156 p.

The role of dopaminergic mechanisms in recovery of function was studied by pharmacological manipulations of the septal irritability syndrome in rats; septal irritability was used as a baseline for comparing effects of pharmacological agents on rate of recovery of affective behavior. It was found that: 1) depletion of catacholaminergic (CA) neurotransmitters in the septal area (SpA) by microinjections of 6-hydroxydopamine (6-OHDA) into septal tissue induces an irritability syndrome; 2) stimulation of CA systems by peripheral injections of CA agents after radio frequency lesions in the SpA results in significant decreases in intensity and duration of the syndrome (L-DOPA, apomorphine, and amphetamine led to complete, irreversible dissipation; methohexital and piribedil led to transient decrease in irritability; theophylline and imipramine-induced transient increases in irritability); 3) contrary to hypothesis, blockade of postsynaptic CA receptors in rats recovered from septal irritability by pimozide does not result in a temporary return of irritability; and 4) chronic presurgical treatment with apomorphine, alpha-methyl-p-tyrosine, morphine, and saline produced irritability after subsequent septal ablation comparable to controls in intensity and duration. It is suggested that many effects of brain-damage might be due to diaschitic processes or to transient dysfunction in adjacent or connected areas and that recovery rate in some experimental and clinical syndromes may be modifiable by pharmacological agents. (Journal abstract modified)

002090 Martin, Gregory E.; Morrison, James E. Department of Medical Neurosciences, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, DC 20012 **Hypothermia evoked by the intracerebral injection of morphine sulphate in the rat: the effect of restraint.** Brain Research (Amsterdam). 145(2):127-140, 1978.

To examine the effect of restraint on morphine evoked hypothermia, morphine sulphate (M) was microinjected intracerebrally into 26 sites in the free moving and 11 sites in the restrained rat. The injections were made into the preoptic/anterior hypothalamic (POAH) region as core temperature (Tc) was measured. A marked increase in T significantly above the control level was observed in the restrained rat following the intracerebral administration of M in doses of 10(n-8), 20(n=9), 50(n=10), or 70(n=4) of Tc micrograms. The control injection of the artificial cerebrospinal fluid (5 ion), used as the drug vehicle, caused a mild hyperthermia about 1.0degree C above the baseline level in both the free moving and restrained rat. It is concluded that morphine evokes a hyperthermia by its action on POAH neurons, but the morphine-induced hyperthermia can be attenuated by restraining the rat. 32 references. (Author abstract modified)

002091 Matsuzaki, Masaji; Whitlock, Eileen G.; Mule, Salvatore J. Research Laboratory, New York State Office of Drug Abuse Services, Brooklyn, NY 11217 **Alterations of EEG activities and cocaine-induced convulsions following prolonged cocaine treatment in the rhesus monkey.** Federation Proceedings. 36(3):411, 1977.

Effects of prolonged cocaine treatment on EEG and cocaine-induced convulsions in rhesus monkeys were reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. A minimal convulsant dose of cocaine was given i.v. daily, 5 days/week, and EEG was recorded. Following 3 or 4 months of cocaine treatment, daily convulsions markedly decreased and stabilized at a constant level along with the onset of convulsions. During this period, the multiple phases of intermittent convulsions changed to the single phase of sustained tonic/clonic convulsions. The monkeys became gentle and inactive or were profoundly depressed most of the time. Persistent rhythmic slow-waves of 5 or 6/sec were observed in the EEG from the neocortex and limbic structures after prolonged cocaine treatment. 1 reference. (Journal abstract modified)

002092 McCulloch, James; Deshmukh, Vinod D.; Harper, A. Murray. Wellcome Surgical Research Inst., Univ. of Glasgow, Garscube Estate, Beardson Rd., Glasgow G61 1QH, Scotland **Indirect sympathomimetic agents and cerebral blood flow and metabolism.** European Journal of Pharmacology (Amsterdam). 47(1):11-18, 1978.

The effects upon cerebral blood flow and oxygen consumption of the infusion into the internal carotid artery of tyramine and amphetamine were investigated in anesthetized baboons (n=24). The infusion of tyramine was without any effect upon cerebral flow and oxygen consumption at normocapnia. However, marked reductions in cerebral blood flow were noted at hypercapnia during the infusion of tyramine. The infusion of amphetamine resulted in significant increases in cerebral blood flow (32%) and oxygen consumption (37%). However, an increased concentration of amphetamine significantly reduced cerebral blood flow (22%) and oxygen consumption (20%). It is suggested that amphetamine by virtue of being able to cross the blood-brain barrier and interact with the cerebral monoamine systems is able to influence cerebral blood flow by inducing changes in cerebral metabolism, and that the minimum reactivity of the cerebral circulation to the infusion of tyramine is the result of the inability of tyramine to cross the blood-brain barrier. 28 references. (Author abstract modified)

002093 McGeer, E. G.; Singh, V. K.; Parkinson, J.; Scherer, U. Division of Neurological Sciences, Dept. of Psychiatry, University of British Columbia, Vancouver, B.C. V6T 1W5, Canada **Effects of morphine on axonal transport in nigrostriatal neurons.** Experimental Neurology. 59(2):342-350, 1978.

To examine effects of morphine on axonal transport in nigrostriatal neurons, axonal transport of labelled protein was compared in controls and in rats treated with morphine by acute i.p. injection or by chronic morphine pellet implants. No significant differences in axonal transport in the nigrostriatal tract were found between controls and test animals. Rats chronically treated with morphine gave more variable results in all tests than the controls but the results did not seem to correlate with the observable behavioral effects. The difference between these results and the significant increase in protein transport reported by others in morphine dependent animals may depend on the lower doses of morphine used in the present experiments. The animals, however, seemed dependent as judged by their response to a naloxone challenge. There was also no significant difference between morphine treated and control rats in the activities of tyrosine hydroxylase, acetylcholinesterase, monoamine oxidase, dopa decarboxylase, or glutamic decarboxylase in the striatum or of glutamic decarboxylase or tyrosine hydroxylase in the substantia

nigra. Striatal choline acetyltransferase was elevated in the rats chronically treated with morphine as previously reported by others. 15 references. (Author abstract modified)

002094 McNulty, Josephine; Leonard, B. E. Dept. of Pharmacology, University College, Galway, Ireland **The acute effects of amphetamine, chlorpromazine, amitriptyline and lithium on adenosine 5-triphosphatase activity in the cortex of the rat brain.** Biochemical Pharmacology (Oxford). 27(1):132-133, 1978.

The effects of acute intraperitoneal injection of amphetamine, chlorpromazine, amitryptyline, and lithium on the activity of sodium, potassium dependent adenosine-5-triphosphatase (Na+,K+-ATPase) and of magnesium dependent ATPase (Mg++-ATPase) in the cortex of the rat brain were investigated, to determine whether the effects of these drugs on these enzymes might be related to these drugs' effects on biogenic amine uptake. In the synaptosomal fraction, chlorpromazine decreased the Na+,K+-ATPase activity and lithium decreased both the Mg++-ATPase activity and the Na+,K+-ATPase activity. Neither amitriptyline nor amphetamine significantly changed the activities of the enzymes. In the vesicular fraction, none of the drugs significantly affected either enzyme. It is considered unlikely that changes in ATPase activities in these subcellular fractions are causally related to the effects of these drugs on the uptake of biogenic amines. 15 references.

002095 Meisheri, Kaushik D.; Isom, Gary E. Dept. of Pharmacology, Faculty of Pharmaceutical Sciences, Univ. of British Columbia, Vancouver, B.C., Canada **Influence of immune stimulation and suppression on morphine physical dependence and tolerance.** Research Communications in Chemical Pathology and Pharmacology. 19(1):85-99, 1978.

The role of the immune system in the development of physical dependence and tolerance to morphine was studied in mice in which the immune response was either stimulated or suppressed. Immunization of mice against morphine increased the blood and brain levels of morphine as compared to controls. However, the development of physical dependence and tolerance was decreased. The chronic responses to morphine were also decreased by nonspecific immunosuppression (vincristine cyclophosphamide treatment and gamma irradiation exposure) and specific immunosuppression (antithymocyte and antilymphocyte sera treatment). Immunosuppressive treatments did not alter the rate of morphine absorption from the subcutaneous depot used to induce chronic exposure to the drug. However, the blood and brain levels of morphine were higher than control after 72 hours of morphine pellet implantation. It is apparent that manipulation of the immune system can alter the physical dependence and tolerance development to morphine. 35 references. (Author abstract)

002096 Meltzer, Herbert Y.; Fang, Victor S.; Fessler, Richard; Simonovic, Miljana; Stanisik, Dusanka. Dept. of Psychiatry, Pritzker School of Medicine, University of Chicago, Chicago, IL 60637 **Neuroleptic-stimulated prolactin secretion in the rat as an animal model for biological psychiatry: I. comparison with anti-psychotic activity.** In: Hanin, I., Animal models in psychiatry and neurology. Elmsford, N. Y., Pergamon Press, 1977. 499 p. (p. 443-454).

In a paper presented at a workshop on animal models in psychiatry and neurology held in Rockville, Maryland, in June 1977, the determination of drug stimulated prolactin secretion in rats as an animal model for the investigation of antipsychotic activity was proposed. Studies are reviewed which indicate that: 1) prolactin secretion from the anterior pituitary gland in the rat is under tonic inhibition by dopamine (DA); 2) the action of DA is probably exerted directly at the pituitary; 3) blockade of DA receptors by neuroleptics produces a marked stimulation of prolactin secretion; 4) drugs with antipsychotic activity increase plasma prolactin; 5) those compounds not having antipsychotic activity do not increase plasma prolactin, with the possible exception of metoclopramide and perlapine, which have been reported to lack antipsychotic activity; 6) metabolites of chlorpromazine which do not inhibit amphetamine-induced stereotypy do not increase plasma prolactin levels; 7) the antipsychotic effects of butaclamol and flupenthixol stereoisome parallel their prolactin secretion stimulating potencies; 8) the ability of a wide variety of antipsychotic drugs to stimulate prolactin secretion is highly correlated with the clinical antipsychotic potency; and 9) no tolerance develops to either the antipsychotic action of drugs or to their ability to stimulate rat or human prolactin secretion. It is suggested that the pituitary DA receptors which regulate prolactin secretion can serve, with due caution, as an animal model for further study of selected features of the DA receptors which mediate the antipsychotic action of neuroleptic drugs in man. 101 references. (Author abstract modified)

002097 Messing, Rita B.; Flinchbaugh, Cort; Waymire, Jack C. Dept. of Psychobiology, Univ. of California, Irvine, CA 92717 **Tryptophan and 5-hydroxyindoles in different CNS regions following acute morphine.** European Journal of Pharmacology (Amsterdam). 48(1):137-140, 1978.

To determine whether morphine induced elevation in tryptophan plays a role in opiate analgesia, tryptophan and 5-hydroxyindoles were measured in different areas of the CNS following acute morphine administration. It was hypothesized that if elevations in tryptophan and 5-hydroxyindoles occur in the same loci, then the likelihood is increased that the rise in precursor availability is related to elevations in 5-hydroxyindoles. Results indicate that morphine induces naloxone reversible increases of tryptophan and 5-hydroxyindoles in rat cerebral hemispheres, thalamus and cerebellum, but does not do so in striatum, hypothalamus, hippocampus and brainstem. Morphine also induces a rise in spinal cord, 5-hydroxyindoleacetic acid (5-HIAA) which is antagonized by naloxone, but there is no parallel change in tryptophan. It is suggested that increases in brain 5-hydroxyindoles may be related to greater availability of tryptophan, but the elevation in spinal cord 5-HIAA appears to be unrelated to precursor availability. 12 references. (Author abstract modified)

002098 Mims, Robert B. Dept. of Medicine and Endocrinology, LAC/USC Medical Center, 1200 North State St., Los Angeles, CA 90033 **Suppression of the hypothalamic-pituitary-adrenal axis after oral hydrocortisone succinate ingestion in rats.** Journal of the National Medical Association. 70(1):37-40, 1978.

To study the responsiveness of the hypothalamic/pituitary/adrenal axis to acute stress, groups of Holtzman female rats were fed orally 10 mg/day of hydrocortisone succinate. Pituitary ACTH content, plasma ACTH, adrenal venous corticosterone, and adrenal weights were studied simultaneously in experimental and control rats before, during, and up to two weeks after oral hydrocortisone administration. There was a significant decrease in pituitary ACTH content, suppression of plasma ACTH and corticosterone in response to acute stress, and adrenal atrophy during and following oral hydrocortisone administration. After discontinuing the hydrocortisone it required 3 to 5 days for the rats to respond adequately to acute stress. It was 7 to 10 days posthydrocortisone before

plasma ACTH and corticosterone responses to acute stress had returned to basal values, but decreased pituitary ACTH content and partial adrenal atrophy continued throughout the ten day posthydrocortisone study interval. Recovering from the suppressive effects of oral hydrocortisone was more rapid than following parenteral hydrocortisone. It was concluded that oral hydrocortisone causes identical but less sustained suppression of the hypothalamic/pituitary/adrenal axis as observed in animals treated with parenteral flucocorticoid preparations. 12 references. (Author abstract)

002099 Mishra, Ram K. Neuropharmacology Laboratory, Department of Psychiatry, McMaster University Medical Center, Hamilton, Ontario, Canada **Pre and postsynaptic effects of sulpiride and other substituted benzamides.** Federation Proceedings. 36(3):319, 1977.

The effect of sulpiride, metoclopramide, and tigan on presynaptic and postsynaptic dopaminergic activity in an unmentioned organism using synaptosomal tyrosine hydroxylase and dopamine sensitive adenylate cyclase will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Tyrosine hydroxylase activity was determined by conversion of labeled tyrosine to catecholamines, and adenylate cyclase activity was determined in caudate homogenate. Apomorphine caused potent inhibition of striatal tyrosine hydroxylase activity in a synaptosomal preparation, and this effect was reversed by haloperidol, sulpiride, metoclopramide, and tigan. The adenylate cyclase activity was unaffected by these drugs with the exception of haloperidol, which caused significant inhibition at low concentrations. Thus, some antipsychotic drugs may interfere selectively with presynaptic dopaminergic mechanisms. 2 references. (Journal abstract modified)

002100 Mobley, Philip L.; Smith, Howard A.; Sulser, Fridolin. Vanderbilt University School of Medicine, Nashville, TN 37232 **Modification of the noradrenergic cyclic AMP generating system in the rat limbic forebrain by amphetamine (A) and its hydroxylated metabolites.** Federation Proceedings. 36(3):319, 1977.

A study of the effect of amphetamine and its metabolites on cyclic AMP response in the limbic forebrain bundle of the rat will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Administration of amphetamine b.i.d. i.p. for 2 to 4 days caused a reduction of cyclic AMP response to norepinephrine in slices of rat limbic forebrain, but did not alter the basal levels of cyclic AMP. Enantiomers of p-hydroxyamphetamine and p-hydroxynorephedrine were studied on the norepinephrine receptor coupled adenylate cyclase system in the limbic forebrain bundle. Most of the p-hydroxynorephedrines were devoid of agonist activity, while all hydroxylated metabolites with one exception potentiated cyclic AMP response to norepinephrine. The enhanced norepinephrine receptor interactions elicited by hydroxylated metabolites of amphetamine may contribute to desensitization of norepinephrine receptors in the brain following repeated administration of amphetamine which, in turn, may be responsible for the development of tolerance to the noradrenergic central actions of amphetamine. 1 reference. (Journal abstract modified)

002101 Moniuszko-Jakoniuk, J.; Koscielak, M.; Wisniewski, K. Dept. of Pharmacology & Radiobiological Research Center, Medical School, Mickiewicza 2, 15-222 Bialystok, Poland **Investigations into the mechanism of the influence of kinins on the action of amphetamine.** Pharmacology (Basel). 16(2):89-97, 1978.

In a study of the effects of kinins on the central action of amphetamine, it was found that bradykinin or activation of the kinin forming system under the influence of kallikrein decreases the psychostimulatory effects of amphetamine given in a small dose (0.5mg/kg) and increases the action of larger doses of amphetamine (2 and 10mg/kg). It was shown that these effects may depend upon the influence of kinins on the level of neuromediators in the CNS after injection of 0.5and 2mg/kg of amphetamine. In comparison with a group of animals receiving only amphetamine, bradykinin given together with amphetamine at a dose of 0.5mg/kg decreased the level of norepinephrine and increased the serotonin level in the corpus striatum; it decreased the level of dopamine in the brain cortex. On the other hand, this peptide given together with amphetamine at a dose of 2mg/kg increased the level of norepinephrine in the hippocampus, of dopamine in the corpus striatum and hippocampus, and also caused a fall in the level of serotonin in the midbrain, as compared with a group of animals given amphetamine only. Investigations with platelets as a model showed that bradykinin may have a bidirectional effect on the uptake of norepinephrine by the nerve endings, depending on the concentration of amphetamine. 24 references. (Author abstract modified)

002102 Morgan, M. E.; Gibb, J. W. Department of Pharmacology, University of Utah, Salt Lake City, UT 84132 **Comparison of the effects of methamphetamine and neuroleptic agents on tyrosine hydroxylase activity in the nucleus accumbens and corpus striatum.** Federation Proceedings. 36(3):383, 1977.

Reduction of tyrosine hydroxylase activity by methamphetamine and reversal of the methamphetamine-induced decrease by haloperidol and chlorpromazine in rat corpus striatum and nucleus accumbens were reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Drugs were administered to rats every 6 hr for 30 hr, and the animals were decapitated 7 or 8 hr after the last injection. In the control groups striatal tyrosine hydroxylase activity was about 50% higher than in the nucleus accumbens. Methamphetamine decreased enzyme activity in the corpus striatum 58% and in the nucleus accumbens 74%. Haloperidol and chlorpromazine alone did not change enzyme levels significantly, but in combination with methamphetamine prevented the methamphetamine-induced decrease in tyrosine hydroxylase activity in both sites. (Journal abstract modified)

002103 Morgan, W. W.; Huffman, R. D.; Pfeil, K. A.; Gonzales, E. G. Department of Anatomy, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284 **Effect of synthesis inhibition on the levels of brain catecholamines in barbital-dependent rats.** Psychopharmacology (Berlin). 56(1):41-44, 1978.

To examine the effect of synthesis inhibition on the levels of brain catecholamines in barbital dependent rats, adult male Sprague-Dawley rats were made barbital dependent by the long-term consumption of increasing concentrations of this compound in their drinking water and the rats were sacrificed immediately or 1 or 2 days following barbital withdrawal. Some animals in each of these groups as well as control animals were treated with alpha-methyl-p-tyrosine (250mg/kg) (aMPT) or FLA-63 (40mg/kg) 2 hr before sacrifice. Following sacrifice, the telencephalon and brainstem of each animal were collected for subsequent analysis of dopamine (DA) and noradrenaline (NA) concentration. No changes in NA concen-

tration were observed in either brain area of any of the experimental groups. On the other hand, when compared to the same parameter in control rats, the depletion of NA produced by aMPT or by FLA-63 pretreatment was significantly greater in the telencephalons of rats following 1 day of barbital withdrawal. Compared to control animals, the depletion of NA after FLA-63 pretreatment was also significantly greater in the brainstems of rats 1 and 2 days following barbital withdrawal. The concentration of DA in the telencephalons of drug dependent rats was significantly decreased when compared to the levels in control animals by the second day of barbital withdrawal. The present data are consistent with an increase in utilization of brain NA and perhaps DA following the abrupt withdrawal of barbital from dependent rats. Further studies are required to determine if these changes in the brain catecholamines are a significant factor in the manifestation of the barbiturate abstinence syndrome. 9 references. (Author abstract modified)

002104 Morgan, W. W.; Pfeil, Karla A.; Gonzales, Elpidia G. University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284 **Effect of alpha-methyl-p-tyrosine on the incidence of spontaneous convulsions observed following barbital withdrawal.** Neuropharmacology (Oxford). 17(2):115-119, 1978.

To examine the effect of alpha-methyl-p-tyrosine (aMPT) on the incidence of spontaneous convulsions following barbital withdrawal, male Sprague-Dawley rats were made dependent on barbital by the administration of this drug in the drinking water following an established dosage regimen. Groups of these animals were treated with saline or 30, 60, 125 or 250mg/kg aMPT at the time of barbital withdrawal and a second time 16 hr later. A statistically significant dosage related decrease in the incidence of withdrawal related convulsions was observed in all of the aMPT treated groups. Only the highest accumulative dosage of aMPT (500mg/kg) produced any evidence of hypothermia. Pretreatment with the same dosages of aMPT did not affect pentylenetetrazol-induced convulsions indicating that aMPT in these concentrations possesses no general anticonvulsant properties. All of the dosages of aMPT utilized were capable of significantly decreasing whole brain levels of dopamine and noradrenaline, at least for a few hours. The results show that aMPT decreases the incidence of convulsions associated with barbital withdrawal and suggest that catecholamines may have a role in the manifestation of the barbiturate abstinence syndrome. 10 references. (Author abstract modified)

002105 Morley, David C.; Galbraith, Peter R. Medical School, Queens Univ., Kingston, Ontario, Canada **Effects of lithium on granulopoiesis in culture.** Canadian Medical Association Journal (Ottawa). 118(3):288-290, 1978.

In a study undertaken to determine how lithium acts, colony forming cells uncontaminated by monocytes (which elaborate colony stimulating factor (CSF) in vitro) were obtained by means of a two step cell separation procedure. The effects of lithium on colony formation were then studied in cultures stimulated by humoral CSF, cultures in which monocytes were relied upon to synthesize CSF de novo and unstimulated cultures. Lithium enhanced the action of CSF but did not stimulate colony formation in the absence of CSF. In monocyte stimulated cultures, colony formation increased with lithium concentrations up to 1 mmol/L but this increase paralleled that in CSF-stimulated cultures and therefore was not due to increased CSF production by monocytes. At higher concentrations of lithium, colony formation decreased in the monocyte-stimulated cultures but increased in the CSF stimulated cultures. A lithium concentration of 4mmol/L gave the greatest enhancing effect on colony formation in CSF stimulated cultures and a concentration greater than 1mmol/L inhibited de novo synthesis of CSF by monocytes. 18 references. (Author abstract)

002106 Murrin, L. Charles; Enna, S. J.; Kuhar, Michael J. Dept. of Pharmacology, Johns Hopkins University School of Medicine, 725 North Wolfe Street, Baltimore, MD 21205 **Autoradiographic localization of (3H)reserpine binding sites in rat brain.** Journal of Pharmacology and Experimental Therapeutics. 203(3):564-574, 1977.

To identify, at a histochemical level, the loci of persistently bound reserpine in the rat central nervous system, (3H)reserpine was administered to rats and they were killed 7 days later. At this time, the regional localization of radioactivity paralleled the distribution of specific binding sites observed in other laboratories. Autoradiographic studies of certain areas displayed a striking localization of radioactivity. There was a marked association of autoradiographic grains with areas containing catecholamine systems. In particular, the locus ceruleus, the caudate putamen, the nucleus accumbens, the dorsolateral septum and the infundibulum had high grain densities. In the caudate putamen, there was a clear localization of grains to the neuropil. There was also a striking association of autoradiographic grains with certain hypothalamic nuclei; i.e.,the dorsal premammillary nucleus, the prelateral mammillary nucleus and the lateral mammillary nucleus. In these areas, the grains were clearly localized in the cytoplasm of the cell bodies. All of the above localizations of autoradiographic grains were blocked by administration of unlabeled reserpine before injection of (3H)reserpine. The significance of these findings and their relationship to the clinical actions of reserpine are discussed. 44 references. (Author abstract modified)

002107 Myslinski, Norbert R.; Anderson, Edmund G. Dept. of Pharmacology, Univ. of Maryland, College of Dentistry, Baltimore, MD 21201 **The effect of serotonin precursors on alpha- and gamma-motoneuron activity.** Journal of Pharmacology and Experimental Therapeutics. 204(2):19-26, 1978.

To test the effects of the 5-hydroxytryptamine (5-HT) precursors, 5-hydroxytryptophan (5-HTP) and tryptophan on alpha and gamma motoneuron discharges in the spinal cat with a deafferented cord, a study was conducted. Injection of 5-HTP resulted in a doubling of the spontaneous discharge rate of gamma-motoneurons and the induction of spontaneous alpha-motoneuron activity. These effects of 5-HTP were reversed by the 5-HT antagonists, cinanserin and methysergide. Tryptophan alone exhibited minimal effects of motoneuron activity, but in animals pretreated with pargyline it significantly excited alpha and gamma-motoneurons. Recordings of alpha and gamma-motoneuron activity in gastrocnemius and semitendinosus nerves revealed that 5-HTP increased alpha and gamma-motoneuron activity in both flexor and extensor nerves. Reversal of the effects of 5-HTP by 5-HT antagonists suggests that these effects were mediated by 5-HT. The observation of 5-HTP effects in preparations with an open gamma-loop indicates that the effects on the alpha-motoneurons are not mediated via the gamma-motoneuron facilitation, but results from a central activiation. 27 references. (Author abstract)

002108 Nagayama, Haruo; Takagi, Akinori; Tateishi, Toshiaki; Takahashi, Ryo. Dept. of Neuropsychiatry, Nagasaki University School of Medicine, Nagasaki 852, Japan **Circadian**

susceptibility rhythm to neuroleptics: tetrabenazine. Psychopharmacology (Berlin). 55(1):61-66, 1977.

To clarify the influences of situational factors on the effects of psychotropic drugs, the sedative effects of tetrabenazine after injection at various times of the day were studied. When 50mg/kg bodyweight of tetrabenazine was injected into rats at eight different times of the day, a circadian rhythm of sedative effect was observed with a peak sedative time of 1490 min at 10:30 and a nadir of 736 min at 07:30. With 10mg/kg bodyweight of tetrabenazine a similar circadian rhythm of sedative effect was observed. This rhythm did not appear to be due to differences of metabolism of tetrabenazine in the tissues, but rather to be closely related to daily fluctuation of serotonin synthesis and release in the brain. 28 references. (Author abstract)

002109 Nagy, Adam. Dept. II, Lillhagen's Mental Hospital, S-42203, Hisings Bacha 3, Sweden **The kinetics of imipramine-N-oxide in rats.** Acta Pharmacologica et Toxicologica (Kobnhavn). 42(1):68-72, 1978.

The kinetics of imipramine-N-oxide in rats was investigated. Rats were given imipramine-N-oxide as single intramuscular injection and then as repeated oral doses. Results indicate that concentration of imipramine-N-oxide increased simultaneously in the brain and blood reaching a peak 45 minutes after a single dose. Imipramine was the quantitatively predominant metabolite in the blood cells and brain, while desipramine reached a higher concentration than imipramine in the plasma. Samples taken at different times after oral doses during continuous treatment showed fairly constant concentration of imipramine-N-oxide and desipramine in the brain, whereas the concentration of imipramine was more fluctuating. 12 references. (Author abstract modified)

002110 Nakagawara, Michio. Dept. of Neuropsychiatry, Faculty of Medicine, Tokyo Medical and Dental University, Tokyo, Japan **The effect of lithium on serotonin metabolism in the brain of rats with particular attention to its effect under the monoamine altered conditions.** Psychiatria et Neurologia Japonica (Tokyo). 79(5):239-256, 1977.

The effects of lithium on serotonin (5HT) metabolism in the brains of male Wistar albino rats in four different conditions (in 5HT increased and decreased conditions) were investigated. 5HT increases were done with injections of parachlorophenylalanine (PCPA) or PCPA and L-dihydroxyphenylalanine (L-dopa); while the 5HT increased conditions were done with injections of L-5,hydroxytryptophan (L-5HTP) and alpha-methyl para tyrosine (alpha-MT). Results indicated that two hours after injection of lithium, 5HT and 5HIAA remained unchanged relative to control in 3 parts of the brain. Under the 5HT decreased condition, lithium caused no remarkable changes in 5HT but it increased the 5HIAA. Under the 4HT decreased and catecholamine increased condition, lithium caused an increase in 5HT and in 5HIAA. In the 5HT increased condition, 5HT was unchanged but 5HIAA increased. From these and other results, it was concluded that lithium caused no remarkable changes in 5HT metabolism, but it caused increases in 5HIAA concentrations in the diencephalon and other parts of the brain under monoamine altered conditions. This suggests lithium increases 5HT turnover rate in some parts of the brain under monoamine altered conditions. 65 references. (Author abstract modified)

002111 Nakamura, Mitsutaka; Fukushima, Hideaki. R&D Center, Pharmaceuticals Division, Sumitomo Chemical Co., Ltd., Takarazuka, Hyogo 665, Japan **Effect of fludiazepam on turnover of serotonin in mouse brain.** Japanese Journal of Pharmacology (Kyoto). 27(6):905-908, 1977.

The effects of single or repeated doses of fludiazepam on serotonin (5-HT) metabolism in mice were investigated. A single dose of fludiazepam-induced head twitches which were blocked by pretreatment with 5-HT antagonists cyproheptadine and methysergide. In mice treated with a single dose of fludiazepam, the concentration of labeled 5-HT in the brain increased by 40%. Results indicate that single and repeated doses (for 5 days) of fludiazepam induce a decrease in the turnover of brain 5-HT in mice. It is hypothesized that benzodiazepines induce the activation of 5-HT receptors which, by a negative feedback mechanism, lead to a decrease in turnover of brain 5-HT. 18 references.

002112 Nandy, K.; Schneider, F. H. Geriatric Research, Educational and Clinical Center, V.A. Hospital, Bedford, MA 01730 **Effects of dihydroergotoxine mesylate on aging neurons in vitro.** Gerontology (Basel). 2(Supplement 1):66-70, 1978.

In a paper presented at a workshop on experimental pharmacology of hydergine in Basel, December 1976, a research study on the effects of dihydroergotoxine mesylate on aging mouse neurons in vitro is described. C1300 mouse neuroblastoma cells gradually accumulate lipofuscin-like pigment when they are maintained in culture. Findings indicated that pigment formation in cells was reduced by exposure of the cells to lower doses of dihydroergotoxine mesylate which also induced neurite formation and increased protein synthesis. It was concluded that since lipofuscin appears to originate as a result of wear and tear within the cells, the drug probably exerts its beneficial effects by reducing the rate of intracellular wear and tear associated with aging. 17 references. (Author abstract modified)

002113 Nielsen, M.; Braestrup, C. Psychopharmacological Research Laboratory, St. Hans Mental Hospital, Dept. E, DK-4000 Roskilde, Denmark **Chronic treatment with desipramine caused a sustained decrease of 3,4-dihydroxyphenylglycol-sulphate and total 3-methoxy-4-hydroxyphenylglycol in the rat brain.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 300(1):87-92, 1977.

The effects of chronic administration of desipramine (DMI) or imipramine on the endogenous concentrations of the major norepinephrine (NE) metabolites 3,4-dihydroxyphenylglycol sulfate (DOPEG-SO4) and free plus conjugated 3-methoxy-4-hycroxyphenylglycol (total MOPEG) and on the accumulation of these metabolites from radiolabeled NE precursors (tyrosine or dopamine) in whole rat brain were investigated. DOPEG-SO4 was decreased 2 hours and 24 hours after the last dose of DMI (10mg/kg twice daily for 4, 10, or 20 days) or imipramine (10mg/kg twice daily for 10 days). The accumulations of 3H-NE and of total MOPEG were less affected, but decreases were often observed for up to 24 hours following the last drug administration. The results indicate that DMI retains its ability to decrease NE turnover over a period of 20 days of treatment. An increase in NE metabolism to above control levels was observed 48 to 72 hours after the last doses of DMI or imipramine, consisting of increased levels of total 3H-MOPEG and total endogenous MOPEG; DOPEG-SO4 was sometimes concomitantly increased. The increase was more consistent after 10 days or 20 days of treatment than after 4 days of treatment with DMI. It is posited that adaptive changes occur in the NE system after 10 days to 20 days of DMI or imipramine administration. 31 references. (Author abstract modified)

002114 Nielsen, M.; Braestrup, C. Psychopharmacological Research Laboratory, St. Hans Mental Hospital, Dept. E., DK-4000 Roskilde, Denmark **Desipramine and some other antidepressant drugs decrease the major norepinephrine metabolite 3,4-dehydroxyphenylglycol-sulfate in the rat brain.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 300(1):93-99, 1977.

The ortho-methylated and nonortho-methylated end metabolites of norepinephrine (NE) in the rat brain were measured to investigate a presumed shift in NE metabolism from intraneuronal to extraneuronal metabolism by uptake inhibitory antidepressant drugs. Desipramine (DMI), protriptyline, and maprotiline reduced the concentration of the major nonortho-methylated NE metabolite 3,4-dihydroxyphenylglycol sulfate (DOPEG-SO4) in the whole rat brain to about 60% to 70% of controls, while imipramine, amitriptyline, butriptyline, and clorimipramine caused no significant decrease. The major ortho-methylated NE metabolite free plus conjugated 3-methoxy-4-hydroxyphenylglycol (total MOPEG) was almost unaffected by all the drugs 2.5hours after administration. At longer time intervals, however, (5 hours) a high dose of DMI decreased total MOPEG to 75% of controls. DOPEG-SO4 was decreased by DMI in all brain regions examined, i.e. cortex, hippocampus, cerebellum, and rest of brain. Radiolabeled noremetanephrine was increased 0.5hour and 1 hour after intraventricular injection of 3H-dopamine; at the same time intervals total 3H-MOPEG and 3H-DOPEG-SO4 were decreased. DMI retained its metabolite lowering effects in reserpinized rats, indicating that amine storage in granules is not necessary for the action of DMI. Inhibition of NE uptake in vivo did not induce the expected increase in the major extraneuronal NE metabolite MOPEG, but only the expected decrease in DOPEG-SO4. The reduction of both the major NE metabolites by DMI suggests a decreased metabolism and turnover of NE. 36 references. (Author abstract modified)

002115 Nistri, A.; Constanti, A. Dept. of Research in Anaesthesia, McGill University, 3655 Drummond Street, Montreal H3G 1Y6, Canada **Effects of flurazepam on amino acid-evoked responses recorded from the lobster muscle and the frog spinal cord.** Neuropharmacology (Oxford). 17(2):127-135, 1978.

The effects of flurazepam hydrochloride on gamina-aminobutyric acid (GABA) or glutamate evoked responses recorded from the lobster muscle fiber and the frog isolated spinal cord were studied using electrophysiological techniques. On lobster muscle, flurazepam (up to 100 microM) reversibly antagonized responses to bath applied or iontophoretically applied glutamate without any effect on GABA responses. Higher concentrations of flurazepam sometimes increased the resting membrane conductance, an effect different from that of GABA in being insensitive to picrotoxin. In the tetrodotoxin (TTX) treated frog spinal cord flurazepam reversibly antagonized both glutamate and GABA evoked dorsal root depolarizations although a smaller dose clearly potentiated the action of GABA. It is suggested the flurazepam antagonized amino acid responses by blocking receptor activated Na+ channels on the postsynaptic membranes. However, the potentiation of GABA action on the frog spinal cord may have involved either release of endogenous GABA or sensitization of spinal receptors to GABA, an action easily obscured by the predominant antagonistic effect of flurazepam at higher concentrations. 40 references. (Author abstract)

002116 Norcross, K.; Spehlmann, R. Northwestern University Medical School, Chicago, IL 60611 **Facilitatory and depressant effects of dopamine in the feline caudate nucleus.** Federation Proceedings. 36(3):516, 1977.

Effect of dopamine on synaptic responses in the cat caudate nucleus was discussed at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. After stereotaxic positioning of eight barreled micropipettes in the head of the caudate nucleus of encephale isole cats, extracellular neuronal action potentials were recorded through the center barrel while drugs were applied by iontophoresis through the surrounding barrels. Stimulation of the caudate nucleus elicited three to five action potentials 7 to 25 msec later. In more than half the neurons tested, dopamine facilitated response to caudate nucleus stimulation in a dose dependent manner, while in 10% of the neurons, dopamine had no effect, and in the remainder dopamine had a depressant effect. In neurons facilitated by dopamine, simultaneous chlorpromazine and haloperidol competitively antagonized the dopamine effect, but when given alone they depressed the response to caudate nucleus stimulation. In neurons depressed by dopamine, haloperidol and chlorpromazine competitively blocked the dopamine depressant effect, while application of the drugs separately facilitated response to caudate nucleus stimulation. (Journal abstract modified)

002117 North, Murray Alan. Department of Psychology, McGill University, 1205 McGregor Avenue, Montreal, Quebec H3A 1B1, Canada **Naloxone reversal of morphine analgesia but failure to alter reactivity to pain in the formalin test.** Life Sciences (Oxford). 22(4):295-302, 1978.

Experiments were performed to ascertain whether naloxone could alter short-term or long-term course of reactivity to formalin-induced pain in morphine treated and untreated rats. Rats received a subdermal injection of dilute formalin into the forepaw and the degree to which the rat favored this was rated on an objective four point scale. Rats treated with naloxone in doses sufficient (10mg/kg) to completely antagonize morphine analgesia showed no decrease in their thresholds of reactivity to formalin-induced chronic pain. The hypothesis that tonic release of endogenous opioids acting at naloxone sensitive receptors decreases sensitivity or reactivity to pain stimuli was not supported. 16 references. (Author abstract modified)

002118 North, R. Alan; Zieglgansberger, Walter. Department of Neuropharmacology, Max-Planck-Institut fur Psychiatrie, D-8 Munchen 40, Germany **Opiate withdrawal signs in single myenteric neurones.** Brain Research (Amsterdam). 144(1):208-211, 1978.

To examine possible manifestations of morphine tolerance and dependence at the single neuronal level, extracellular recordings were made from single guinea-pig myenteric neurones from naive and morphine dependent animals in the presence of normorphine alone or with naloxone. In preparations taken from naive animals, normorphine caused an immediate and complete inhibition of spike firing in the greater majority of spontaneously firing neurones. In preparations from dependent animals, this depression in firing did not occur indicating that tolerance had developed. Application of naloxone to dependent animal preparations resulted in an increase in firing rate. In almost all experiments naloxone caused additional cells to fire which had been previously quiescent. Further, naloxone caused violent contractions of the longitudinal muscle underlying the ganglion. Atropine largely prevented these muscle contractions while not affecting the rate of firing. Findings strongly suggest that manifestations of morphine tolerance and dependence are produced at the level of the single mammalian neurons. 18 references.

002119 Northrup, Thomas E.; Kim, Jin K.; Heublein, Denise M.; Dousa, Thomas P. Mayo Clinic and Foundation, Rochester, MN 55901 **Influence of triiodothyronine (T3) on the renal action of lithium.** Federation Proceedings. 36(3):604, 1977.

A paper presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977, reports investigation of the role of triiodothyronine in LiCl-induced salt loss and water loss. Because administration of lithium chloride causes both depression of thyroid function and marked solute and water diuresis the effects of LiCl on hypothyroid rats were studied. All rats were thyroidectomized on day 1. On days 12 to 29 one group of rats received replacement doses of triiodothyronine, while another group received vehicle only. All rats received LiCl on days 16 to 29. On days 12 to 16 urine flow, sodium excretion, and potassium excretion were similar in both groups. Beginning on day 17, the experimental rats had higher levels of urine flow, and excretion of sodium, potassium, and phosphate. Lithium excretion did not differ between the two groups. On day 29, there were no differences between groups in plasma concentrations of sodium, potassium, creatinine, urea nitrogen, or tissue concentrations of sodium or water. Plasma lithium in the treated group was half that of the control group. Thus the effects of thyroid function on lithium-induced changes in salt and water balance occur at the level of the kidney. (Journal abstract modified)

002120 Nowycky, Martha C.; Roth, Robert H. Dept. of Pharmacology, Yale University School of Medicine, New Haven, CT 06510 **Presynaptic dopamine receptors: development of supersensitivity following treatment with fluphenazine decanoate.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 300(3):247-254, 1977.

An in vivo model for investigating the interaction of drugs with presynaptic receptors was used to study the effect of chronic treatment of rats with fluphenazine decanoate on the presynaptic dopamine receptors in the neostriatum and olfactory tubercle. In this model system dopaminergic impulse flow is inhibited pharmacologically with gamma butyrolactone (GBL), resulting in an increase of apparent tyrosine hydroxylase activity. On days 12 through 21 after rats were injected with fluphenazine decanoate, dopamine agonists apomorphine (tested on days 12, 15, 17, and 21) and trivastal (ET 495; piribidil; tested on days 12, 14, and 19) were more potent in blocking the GBL-induced increase of dopa accumulation in the striata of treated animals than in controls. Thirty days after the fluphenazine injection the effect of the dopamine agonists on dopa accumulation in the neostriatum returned to control levels. In control animals apomorphine was approximately 10 fold more potent in depressing the GBL-induced increase of dopa accumulation in the olfactory tubercles than in the neostriatum. Apomorphine was even more potent in the olfactory tubercle on day 14 after a single injection of fluphenazine decanoate. These results suggest that following chronic treatment of rats with a phenothiazine, presynaptic receptors on dopamine nerve terminals in the striatum and limbic system become supersensitive to dopamine agonists. 25 references. (Author abstract modified)

002121 Nozaki, Masako; Vaupel, Donald B.; Martin, William R. Dept. of Pharmacology, Cornell University Medical College, New York, NY **A pharmacologic comparison of 3,4-methylenedioxyamphetamine and LSD in the chronic spinal dog.** European Journal of Pharmacology (Amsterdam). 46(4):339-349, 1977.

3,4-Methylenedioxyamphetamine (MDA), in doses of 2.0and 2.2mg/kg was compared to LSD, 10 micrograms/kg, and d-amphetamine, 3.2mg/kg, in single doses, antagonism, cross-tolerance and appetite suppression studies in chronic spinal dogs. In single doses, MDA specifically resembed d-amphetamine by producing marked mydriasis, nictating membrane retraction, stereotypy and darting eye movements; it resembled LSD by markedly facilitating the flexor reflex, producing continuous stepping, whining, and eye tracking movements. LSD and MDA increased respiration, body temperature, and the latency of the skin twitch reflex and produced behavioral arousal. Cyproheptadine antagonized the effects of LSD but was ineffective against MDA. Phenoxybenzamine antagonized the respiratory, pupillary, and hyperthermic effects of MDA and the respiratory effect of LSD. Chlorpromazine antagonized many effects of LSD and MDA. Spinal dogs were made tolerant to the behavioral and physiologic effects of LSD. Cross-tolerance developed to some but not all of the effects of MDA. In intact dogs, MDA was one tenth as potent as d-amphetamine in suppressing appetite. It is concluded that MDA has properties resembling both LSD and amphetamine. 23 references. (Author abstract modified)

002122 Olsen, R. W.; Ticku, M. K.; Van Ness, P. C.; Greenlee, D. Dept. of Biochemistry, University of California, Riverside, CA 92521 **Effects of drugs on gamma-aminobutyric acid receptors, uptake, release and synthesis in vitro.** Brain Research (Amsterdam). 139(2):277-294, 1978.

The effects of various convulsant and anticonvulsant drugs have been studied using in vitro assays for the postsynaptic action of the neurotransmitter gamma-aminobutyric acid (GABA). GABA caused a receptor ionophore mediated increase in chloride permeability in crayfish muscle. At 100 microMole concentrations, benzyl penicillin, bicuculline, diethyl barbiturate, diazepam, imipramine, and haloperidol partially inhibited this response while picrotoxinin inhibited it 100%. Muscimol (potently) and beta-p-chlorophenyl-GABA (weakly) mimic GABA action in this assay. Muscimol and bicuculline (potent), and benzyl penicillin and beta-p-chlorophenyl-GABA (weak), but not the other drugs, probably exerted their effects at the GABA receptor level, because only these four drugs among those tested were inhibitors of GABA receptor binding sites in mouse brain homogenates (sodium independent sites having the specificity expected of receptor sites). The drugs were also examined for effects on in vitro assays of GABA uptake, glutamate decarboxylase activity (GAD), and Ca2+-stimulated GABA release with mouse brain homogenates. GABA uptake by mouse brain particulate fractions was inhibited 50% by approximately 100 microMole haloperidol, imipramine, chlorpromazine, diazepam, benzyl penicillin, bicuculline, and beta-p-chlorophenyl-GABA, but by muscimol only at concentrations near 1 mM. Analogs of lioresal and muscimol are viewed as promising candidates for treatment of neurological disorders involving GABA dysfunction. 73 references. (Author abstract modified)

002123 Owasoyo, Joseph O.; Whitworth, Ulysses G.; Sollman, Karam F.; Walker, Charles A. School of Pharmacy, Florida A and M University, Tallahassee, FL 32307 **The effects of picrotoxin and pentylenetetrazol in the diurnal rhythms of catecholamines and serotonin in the rat brain.** Federation Proceedings. 36(3):352, 1977.

Paper to be presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977, reports a study of the effects of analeptics on

diurnal levels of catecholamines and serotonin in rat brain. All animals were adapted to a 12 hr light/12 hr dark cycle for at least 3 wks. Acute treatment with sublethal doses of pentylenetetrazol or picrotoxin was found to alter the levels and/or diurunal patterns of norepinephrine, dopamine, and serotonin in the caudate nucleus, cerebellum, cortex, and midbrain. For both analeptic drugs the greatest change in serotonin occurred in the caudate nucleus. Midbrain norepinephrine was affected more by picrotoxin than by pentylenetetrazol. (Journal abstract modified)

002124 Pericic, D.; Walters, J. R.; Chase, T. N. Rudjer Boskovic Institute, 41000 Zagreb, P.O.B. 1016, Yugoslavia **Effect of diazepam and pentobarbital on aminooxyacetic acid induced accumulation of GABA.** Journal of Neurochemistry (Oxford). 29(5):839-846, 1977.

The effects of diazepam and pentobarbital on gamma-aminobutyric acid (GABA) levels, the aminooxyacetic acid (AOAA) induced accumulation of GABA, and the in vitro activity of L-glutamate 1-carboxyl-lyase (GAD) were studied in various regions of rat brain. Diazepam increases GABA levels in the substantia nigra, diminishes the AOAA-induced accumulation of GABA in the caudate nucleus, cingulate, parietal and entorhinal cortex and has no effect on GABA accumulation in the pyriform and cerebellar cortex. After pentobarbital, GABA levels are elevated in the caudate nucleus but decreased in the parietal and pyriform cortex; the AOAA-induced accumulation of GABA also diminishes in all cortical regions studied. The reduction in AOAA-induced GABA accumulation after diazepam and pentobarbital treatment is most pronounced in regions which show the greatest accumulation of GABA after AOAA administration. Neither diazepam nor pentobarbital administration affect the activity of GAD in homogenates of cingulate cortex. Chlorpromazine, at a dose which decreases spontaneous activity, enhances the AOAA-induced GABA accumulation in the cingulate cortex, suggesting that drug-induced sedation is not necessarily associated with decreased GABA synthesis. While regional differences are observed in the effects of diazepam and pentobarbital on GABA synthesis, both agents appear to inhibit GABA synthesis in vivo and both do so, in at least some brain areas, at subsedative doses. 46 references. (Author abstract modified)

002125 Persson, Sven-Ake; Johansson, Hakan. Dept. of Pharmacology, University of Umea, S-90187 Umea, Sweden **The effect of lysergic acid diethylamide (LSD) and 2-bromolysergic acid diethylamide (BOL) on the striatal dopa accumulation: influence of central 5-hydroxytryptaminergic pathways.** Brain Research (Amsterdam). 142(3):505-513, 1978.

Mediation mechanism of striatal DOPA accumulation by LSD was examined in the rat. Results indicate that selective chronic lesions of the dorsal raphe nucleus or combined lesions of the dorsal and median raphe nucleus did not significantly change in vivo tyrosine hydroxylation in the stratium as measured by the DOPA accumulation after decarboxylase inhibition. Neither did acute combined lesions of the raphe nuclei, nor did electrical stimulation of the dorsal raphe nucleus have any significant effect. p-Chloroamphetamine (20mg/kg, ip) and p-chlorophenylalanine (400mg/kg, ip) significantly decreased the DOPA accumulation. The increase in DOPA accumulation observed after LSD (0.5mg/kg, ip) or 2-bromolysergic acid diethylamide was seemingly unaffected by treatment with PCA or p-chlorophenylalanine and also after lesion of the dorsal raphe nucleus. The results suggest that the effect of LSD or 2-bromolysergic acid diethylamide on DOPA accumulation in the stratium is not mediated via 5-hydroxytryptaminergic control mechanism originating in the dorsal raphe nucleus. 28 references. (Author abstract modified)

002126 Pinchasi, Irit; Maayani, Saul; Egozi, Yaakov; Sokolovsky, Mordechai. Department of Biochemistry, George S. Wise Center for Life Sciences, Tel-Aviv University, Tel-Aviv, Israel **On the interaction of drugs with the cholinergic nervous system. II. Cross-tolerance between phencyclidine derivatives and cholinergic drugs.** Psychopharmacology (Berlin). 56(1):37-40, 1978.

To evaluate the contribution of cholinergic interactions to the effects induced by phencyclidine derivatives in vivo, tolerance to phencyclidine, cyclohexamine, physostigmine, or oxotremorine was induced in mice and the development of cross-tolerance to each of the three other drugs was assessed. A symmetrical cross- tolerance was found between two phencyclidine derivatives, phencyclidine and cyclohexamine, and also between two cholinergic drugs, physostigmine and oxotremorine. On the other hand, mice rendered tolerant to the phencyclidine derivatives showed cross-tolerance to these cholinergic drugs, but no cross-tolerance was observed in the opposite direction. The applicability of such experiments to the elucidation of neurochemical interactions of centrally acting drugs is discussed. It is suggested that the existence of symmetrical cross-tolerance between drugs may reflect a common mechanism of action and a common neurochemical pathway. 23 references. (Author abstract modified)

002127 Pinchasi, Irit; Maayani, Saul; Sokolovsky, Mordechai. Department of Biochemistry, George S. Wise Center for Life Sciences, Tel-Aviv University, Tel-Aviv, Israel **On the interaction of drugs with the cholinergic nervous system. I. Tolerance to phencyclidine derivatives in mice: pharmacological characterization.** Psychopharmacology (Berlin). 56(1):27-36, 1978.

Phencyclidine (1(1-phenylcylohexyl) piperidine) and cyclohexamine (1(1-phenylcyclohexyl) ethylamine) were used as model psychotropic drugs to study the phenomenon of tolerance in mice. The behavioral effects of these drugs were measured by forced motor activity using the rotarod test. Tolerance develops progressively with chronic treatment at a rate and to a degree that are dose dependent. The optimal conditions for tolerance induction are subcutaneous administration with 4 hr intervals. The process of tolerance development is expressed in concomitant changes in five indices chosen for its quantification: lethality values, duration, duration/dose dependency, critical falling time, and bodyweight. All these changes were found to be totally reversible, with no carryover between two consecutive tolerance cycles. It was established that cyclohexamine is a better tolerance inducer than phencyclidine, although the nature of the tolerance developed for both drugs is qualitatively similar. The significance of these results with respect to putative biochemical tolerance mechanisms is presented and discussed. 43 references. (Author abstract)

002128 Polc, P.; Haefely, W. Pharmaceutical Research Dept., Hoffman-La Roche, Ltd., CH-4002 Basel, Switzerland **Effects of intravenous kainic acid, N-methyl-D-aspartate, and (-)-nuciferene on the cat spinal cord.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 300(3):199-203, 1977.

Kainic acid (a rigid conformational analogue of glutamate), N-methyl-D-aspartate (the methylated derivative of aspartate), and (-)-nuciferine (an aporphine alkaloid with a depressant effect on glutamate-induced neuronal firing), which, so far, have been examined in microiontophoretic studies, were investigated in spinal cats for their effects on some spinal cord

activities after intravenous injections. At low doses, kainic acid (0.3mg/kg-1) enhanced segmental monosynaptic but not polysynaptic ventral root reflexes and increased the excitability of motoneurones, whereas N-methyl-D-aspartate (3mg/kg-1) facilitated polysynaptic but not monosynaptic reflexes. Higher doses of the two amino acids depolarized motoneurones and primary afferent endings, enhanced monosynaptic reflexes and depressed polysynaptic reflexes. (-)-Nuciferine (1 to 10mg/kg-1) depressed monosynaptic but not polysynaptic ventral root reflexes in a dose dependent manner and antagonzied the effects of kainic acid but not of N-methyl-D-aspartate on the spinal cord. The results are consistent with the hypothetical excitatory transmitter role of glutamate in primary afferents and of aspartate in excitatory spinal cord interneurones; the findings also suggest that (-)-nuciferine may be used as a systematically effective, rather selective blocker of central glutamate receptors. 14 references. (Author abstract)

002129 Polson, James B.; Krzanowski, Joseph J.; Fitzpatrick, David F.; Szentivanyi, Andor. Dept. of Pharmacology, University of South Florida, College of Medicine, Tampa, FL 33612 **Studies on the inhibition of phosphodiesterase-catalyzed cyclic AMP and cyclic GMP breakdown and relaxation of canine tracheal smooth muscle.** Biochemical Pharmacology (Oxford). 27(2):254-256, 1978.

An investigation was undertaken to determine whether a quantitative correlation could be found in respiratory smooth muscle between the phosphodiesterase (PDE) inhibition and muscular relaxation produced by pharmacological agents such as caffeine, which are known to inhibit cyclic-3,5-nucleotide phosphodiesterase(s). Results support the concept that relaxation is produced as a result of pharmacological inhibition of cyclic-3,5-adenosine monophosphate (cAMP) breakdown and the subsequent accumulation of cAMP in cells. Inhibition of cyclic-3,5-guanosine monophosphate (cGMP), a tissue constituent that has been implicated as a stimulator of smooth muscle contraction, can also be correlated with relaxation, although in most cases inhibition of cGMP is not as great as for cAMP. 29 references.

002130 Polzin, Robert L.; Barnes, Charles D. Department of Physiology, Texas Tech University School of Medicine, Lubbock, TX 79409 **The iontophoresis of diazepam in the cuneate nucleus and cerebellar cortex of the cat.** Federation Proceedings. 36(3):289, 1977.

The effect of iontophoresis of diazepam and gamma-aminobutyric acid (GABA) on the cuneate nucleus and the cerebellar cortex in the cat was reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Cats were iontophoresed with diazepam or with the solvent alone, and extracellular potentials were recorded. Diazepam or GABA inhibited spontaneously firing neurons in the cuneate nucleus and cerebellar cortex. Nonspontaneous neurons in the cuneate nucleus which were excited by glutamate were inhibited by GABA or diazepam or both together. Bicuculline, a GABA blocker, blocked the inhibition induced by GABA or diazepam. (Journal abstract modified)

002131 Polzin, Robert Lawrence. Indiana State University **The role of diazepam as compared to gamma-aminobutyric acid (GABA) in the cuneate nucleus and cerebellar cortex of the cat. (Ph.D. dissertation).** Dissertation Abstracts International. Ann Arbor, MI, Univ. M-films, No. 77-20666 HC$15.00 MF$8.50 71 p.

The role of diazepam as compared to gamma-aminobutyric acid (GABA) in the cuneate nucleus (CN) and cerebellar cortex (CC) of the cat was examined in light of evidence that diazepam is agonistic to GABA in the CN and CC and conflicting evidence that diazepam is antagonistic to GABA in CC. Diazepam was dissolved with methane sulfonic acid in water and the pH adjusted to 4; controls were done with solvent alone. Diazepam inhibited the spontaneously firing neurons in the CN and CC, which were also inhibited by GABA. Nonspontaneous neurons in the CN that were excited by the iontophoresis of glutamate were inhibited by GABA or diazepam. When diazepam and GABA were applied simultaneously, an inhibition occurred. The inhibition of spontaneously firing neurons by either GABA or diazepam could be blocked by the iontophoresis of bicuculline or picrotoxin, known GABA blockers in CN. In CC, the inhibition of diazepam was weakly blocked by picrotoxin and bicuculline. No evidence could be found for GABA and diazepam being antagonistic in action. It is concluded that diazepam may be agonistic or synergistic to GABA's action. (Journal abstract modified)

002132 Proudfit, Herbert K.; Levy, Richard A. Dept. of Pharmacology, University of Illinois at the Medical Center, Chicago, IL 60612 **Delimitation of neuronal substrates necessary for the analgesic action of baclofen and morphine.** European Journal of Pharmacology (Amsterdam). 47(2):159-166, 1978.

The loci of neuronal substrates necessary for analgesic action of baclofen and of morphine were determined by systemic transection of the rat cerebrospinal axis. Severe reduction in the analgesic capacity of both drugs, assessed with tail flick test, occurred after section of the spinal cord, indicating that necessary substrates are located rostral to this level. These data also suggest that baclofen-induced analgesia does not primarily result from a pharmacological blockade of nociceptive information at the first sensory synapse in the spinal cord. Neither baclofen- nor morphine-induced analgesia was inferior colliculi, but the action of both drugs was greatly reduced following section of the medulla, 3mm rostral to the obex. It is concluded that the rostral margin of neuronal substrates mediating the analgesic effects of baclofen and morphine lies somewhere in the pons or anterior third of the medulla. 31 references. (Author abstract modified)

002133 Puech, Alain J.; Frances, Henriette; Simon, Pierre. Dept. de Pharmacologie, Faculte de Medecine Pitie-Salpetriere, 91 Boulevard de l'Hospital, F-75634 Paris Cedex 13, France **Imipramine antagonism of apomorphine-induced hypothermia: a non-dopaminergic interaction.** European Journal of Pharmacology (Amsterdam). 47(1):125-127, 1978.

Imipramine antagonism of apomorphine-induced hypothermia was studied in mice. Results indicate that imipramine antagonized high dose apomorphine-induced hypothermia but did not modify small dose apomorphine-induced hypothermia. It is suggested that apomorphine-induced hypothermia is the result of two effects: 1) that which is induced by small doses of apomorphine and antagonized by pimozide and sulpiride is probably related to dopaminergic receptor stimulation; and 2) that which is induced by high doses of apomorphine and antagonized by imipramine is probably not related to dopaminergic receptor stimulation. 5 references. (Author abstract modified)

002134 Quiring, K.; Hubertus, S. Institut fur Arzneimittel, Bundesgesundheitsamt D-1000 Berlin 33, Germany **Monoamine oxidase in rat reticulocytes: subcellular localization and identification of isoenzymes.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 300(3):273-279, 1977.

In a study on subcellular localization and identification of isoenzymes of monoamine oxidase (MAO) in rat reticulocytes, reticulocytosis was induced in rats by treatment with acetylphenylhydrazine, and MAO activities were determined in erythrocyte preparations of these animals. Studies on subcellular fractions obtained by differential centrifugation showed that the enzyme activity of rat reticulocytes is a classical mitochondrial MAO. The patterns of inhibition produced by clorgyline (A-type MAO), deprenil (B-type MAO) and pargyline or tranylcypromine (both types of MAO) in reticulocytes were determined in vitro using tryptamine as a substrate for both types of MAO and phenylethylamine as a substrate for the B-type. The results indicate that both A-type and B-type are present in rat reticulocytes; while tryptamine was mainly deaminated by the A-type enzyme, both types of MAO were shown to contribute to the deamination of phenylethylamine. These findings were confirmed in investigations on the thermostabilities of the tryptamine and phenylethylamine deaminating activities of rat reticulocyte MAO. 38 references. (Author abstract modified)

002135 Quock, R. M. Department of Physiology-Pharmacology, University of the Pacific, Stockton, CA 95211 **"Prodopaminergic" effect of narcotic antagonists in rabbits pretreated with anti-dopaminergic or anti-serotonergic agents.** Federation Proceedings. 36(3):290, 1977.

A study of apomorphine-induced hyperthermia will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Hyperthermia was induced in rabbits by apomorphine i.v.,which evoked a 1.5degree rise in colonic temperature. The hyperthermia was potentiated by naloxone i.v. and intraventricular naloxone and was antagonized by haloperidol i.v.,cyproheptadine i.v.,cinanserin i.v.,and p-chlorophenylalanine i.p. Administration of naloxone i.v. prior to apomorphine enabled apomorphine to overcome all the above antagonisms and restored apomorphine hyperthermia. Naltrexone produced similar interactions with apomorphine. 3 references. (Journal abstract modified)

002136 Ramsey, Robert B.; Fischer, Vernon W. Department of Neurology, St. Louis University School of Medicine, St. Louis, MO 63104 **Effect of 1-aminocyclopentane-1-carboxylic acid (cycloleucine) on developing rat central nervous system phospholipids.** Journal of Neurochemistry (Oxford). 30(2):447-457, 1978.

Treatment of developing rats with 1-aminocyclopentane-1-carboxylic acid (cycloleucine) resulted in changes in brain and spinal cord phospholipid content and fatty acid composition. General findings were a decrease in ethanolamine phospholipid content and relative increase in the saturated fatty acid content of ethanolamine phospholipid. In all the different cycloleucine experiments conducted, there was consistently less fatty aldehyde present in the methylated ethanolamine phospholipid fatty acid/fatty aldehyde fractions than in corresponding controls. In some experiments fatty aldehyde was almost completely absent, suggesting the presence of little plasmalogen. Changes in fatty acids of phosphatidyl choline, the other phospholipid examined in this manner, were generally minor. Administration of massive amounts of sodium propionate in addition to cycloleucine did not result in an appreciable odd chain fatty acid increase in the CNS. Examination of the spinal cords by electron microscopy demonstrated considerable myelin splitting in one set of animals. No other ultrastructural changes were evident. The suitability of this drug to produce a neurological condition and pathological state similar to that seen in B12 deficient subacute combined degeneration is discussed. 33 references. (Author abstract)

002137 Richelson, E. Mayo Foundation, Rochester, MN 55901 **Antipsychotic drugs block muscarinic acetylcholine receptor mediated formation of cyclic GMP in cultured mouse neuroblastoma cells.** Federation Proceedings. 36(3):750, 1977.

Effect of antipsychotic drugs on muscarinic receptors in living mouse nerve cells was reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. A technique was developed to assay receptor mediated formation of cyclic-GMP in intake cells of adrenergic mouse neuroblastoma clone N1E-115 by radioactively labeling intracellular stores of guanosine triphosphate. From parallel displacement of dose/response curves for carbamylcholine in the presence of antagonist, equilibrium dissociation constants were determined. Of the 11 antipsychotic drugs tested, the most potent was clozapine and the least potent was prochlorperazine. Thus, antipsychotic drugs pharmacologically block the muscarinic acetylcholine receptor. (Journal abstract modified)

002138 Robson, Ronald D.; Antonaccio, Michael J.; Saelens, Jeffrey K.; Liebman, Jeffrey. Research Department, Pharmaceuticals Division, Ciba-Geigy Corporation, Summit, NJ 07901 **Antagonism by mianserin and classical alpha-adrenoceptor blocking drugs of some cardiovascular and behavioral effects of clonidine.** European Journal of Pharmacology (Amsterdam). 47(4):431-442, 1978.

Antagonism of pressor responses to sympathetic outflow stimulation and alpha-adrenoreceptor agonists in pithed spontaneously hypertensive rats was used to estimate postsynaptic alpha-adrenoceptor blocking activity of mianserin, phentolamine, phenoxybenzamine, piperoxan and yohimbine. Estimation of presynaptic alpha-adrenoceptor blocking activity of these drugs was obtained by studying their ability to antagonize clonidine-induced suppression of positive chronotropic responses to sympathetic outflow stimulation. Evidence was obtained that mianserin causes selective presynaptic alpha-adrenoceptor blockade. Mianserin, piperoxan and yohimbine antagonized clonidine-induced avoidance blockade or hypotension in spontaneously hypertensive rats, but methysergide, phenoxybenzamine and phentolamine were ineffective. These results suggest that mianserin may antagonize the central effects of clonidine by blockade of noradrenergic presynaptic or autoreceptors and possibly explain the antidepressant effect of mianserin as due to indirect activation of central noradrenergic neurons. 44 references. (Author abstract)

002139 Roizen, Michael F.; Moss, Jonathan; Henry, David P.; Weise, Virginia; Kopin, Irwin J. Dept. of Anesthesia, Univ. of California, San Francisco, CA **Effect of general anesthetics on handling- and decapitation-induced increases in sympathoadrenal discharge.** Journal of Pharmacology and Experimental Therapeutics. 204(1):11-18, 1978.

To test the effect of five anesthetics -- cyclopropane, pentobarbital, urethane, chloralose or ketamine hydrochloride -- on handling or decapitation induced increases in adrenergic tone in the intact rat, a study was conducted. The anesthetic agents tested prevented or markedly reduced stress-induced increases in levels of plasma total catecholamines and norepinephrine. Similar changes in norepinephrine were seen in corticosterone treated adrenalectomized rats in which this catecholamine seemed to be the only one present in plasma. During anesthesia with cyclopropane, blood pressure fell; there was no additional decrease in total plasma

catecholamines when the concentration of the inhaled anesthetic agent was increased. With increased length of cyclopropane anesthesia, however, total catecholamine and norepinephrine concentrations increased. Thus, it was concluded the different effects of anesthetics on the cardiovascular system cannot be solely explained by their effects on stress-induced increases in sympathetic neuronal activity as reflected by circulating catecholamine levels. 30 references. (Author abstract)

002140 Rotenberg, Fred A.; Verrier, Richard L.; Lown, Bernard; Sole, Michael J. Dept. of Pharmacology & Toxicology, University of Rhode Island, Kingston, RI 02881 **Effects of clonidine on vulnerability to fibrillation in the normal and ischemic canine ventricle.** European Journal of Pharmacology (Amsterdam). 47(1):71-79, 1978.

The effects of clonidine on vulnerability to fibrillation in the normal and ischemic ventricle were studied in the dog. Clonidine infusion (10 microgram/kg) elicited a 30% increase in repetitive extrasystole threshold in chloralose anesthetized dogs (n=6). A reduction in heartrate and arterial blood pressure accompanied the increased threshold. Intracisternal injection of clonidine (2 micrograms/kg) caused similar alterations in these parameters. Bilateral vagotomy prior to intravenous clonidine prevented the increase in repetitive extrasystole threshold but did not prevent the drug-induced bradycardia. Atropine (0.2and 0.6mg/kg) did not attenuate the effect of clonidine on repetitive extrasystole threshold. Clonidine administration did not prevent the reduction in ventricular fibrillation threshold associated with a 10 minute occlusion of the left anterior descending coronary artery or following reperfusion. Findings suggest that: 1) clonidine reduces ventricular vulnerability in the normal but not the ischemic heart; and 2) its protective effect is mediated by enhanced afferent vagal input to midbrain cardiovascular regulatory centers. 37 references. (Author abstract modified)

002141 Ruth, James A.; Grunewald, Gary L.; Rutledge, Charles O. Department of Pharmacology and Toxicology, School of Pharmacy, University of Kansas, Lawrence, KS 66045 **Conformationally defined adrenergic agents. III. The importance of compartmentation in the release of norepinephrine from rat atria by endo- and exo-2-methylaminobenzobicyclo-(2.2.2)octene, conformationally defined analogs of methamphetamine.** Journal of Pharmacology and Experimental Therapeutics. 204(3):615-624, 1978.

To probe stereochemical aspects of amphetamine-induced release of l-norepinephrine (NE) from adrenergic nerve terminals of rat atria, the endo (NM-N) and exo (NM-X) isomers of 2-methylaminobenzobicyclo(2.2.2)octene were employed as spatially defined analogs of the "folded" (NM-N) and "extended" (NM-X) conformations of methamphetamine (MA). As compartmentation was changed from primarily extravesicular to primarily vesicular in nature, the ability to release NE from the nerve ending decreased for MA and disappeared for NM-X. NM-N was ineffective in any of these studies. The results suggest that amphetamine probably interacts with the neuronal amine uptake site in the fully extended conformation; which is also involved in the displacement of NE from an extravesicular compartment. In order to displace NE from vesicular storage sites, either conformational mobility or a conformation of MA not approximated by either NM-N or NM-X is required. 27 references. (Author abstract modified)

002142 Rutledge, Charles O. Department of Pharmacology and Toxicology, School of Pharmacy, University of Kansas, Lawrence, KS 66045 **Effect of metabolic inhibitors and ouabain on amphetamine- and potassium-induced release of biogenic amines from isolated brain tissue.** Biochemical Pharmacology (Oxford). 27(4):511-516, 1978.

A series of experiments was undertaken to examine the effects of metabolic inhibitors and ouabain on amphetamine and potassium-induced release of biogenic amines from isolated rat cerebral cortex. Amphetamine-induced release of norepinephrine (NE) was markedly potentiated in the presence of the metabolic inhibitors sodium cyanide, 2,4-dinitrophenol and iodoacetate. Release of NE by the metabolic inhibitors in the absence of amphetamine was minimal. Amphetamine-induced release of dopamine (DA) from corpus striatum was also potentiated by sodium cyanide. Release of NE and dopamine by elevated concentrations of potassium chloride was again potentiated by the metabolic inhibitors. Similarly, ouabain produced minimal release of NE but potentiated amphetamine and potassium-induced release of catecholamines. The metabolic inhibitors markedly reduced the ATP content of the chopped tissue during the incubation while ouabain had no effect. The results suggest that the potentiation of amphetamine and potassium-induced release of biogenic amines from isolated brain tissue is not simply due to depletion of tissue ATP levels but may be related to sodium or potassium transport. A model is described in which norepinephrine and sodium are cotransported across the membrane during amphetamine-induced release of the biogenic amine. 30 references. (Author abstract modified)

002143 Sanfacon, G.; Labrecque, G. Departement de Pharmacologie, Faculte de Medecine, Universite Laval, Ste-Foy, Quebec G1K 7P4, Canada **Acetylcholine antirelease effect of morphine and its modification by calcium.** Psychopharmacology (Berlin). 55(2):151-156, 1977.

To evaluate the possibility of an interactive effect of morphine and calcium on neocortical acetylcholine (ACh) release, the effects of morphine (10mg/kg) and calcium (10mg/kg) were studied on the neocortical release of ACh in ketamine anesthetized rats. Morphine decreases ACh release as measured by the dorsal leech muscle as well as by an enzymatic assay. Calcium is ineffective alone but antagonizes the action of morphine. Results support the hypothesis that the ACh antirelease action of narcotics is mediated through an interaction with calcium. 23 references. (Author abstract modified)

002144 Scatton, Bernard. Synthelabo, Dept. of Biology, Neurochemistry Unit, 31, avenue Paul Vaillant Couturier, F-92220 Bagneux, France **Differential regional development of tolerance to increase in dopamine turnover upon repeated neuroleptic administration.** European Journal of Pharmacology (Amsterdam). 46(4):363-369, 1977.

Regional cerebral development of tolerance to increase in dopamine turnover upon repeated neuroleptic administration was investigated in the rat. Repeated treatment with haloperidol with sulpiride-induced tolerance to increases in homovanillic and dihydroxyphenylacetic acids in striatum, nucleus accumbens, tuberculum olfactorium and frontal cortex of the rat. The threshold dose inducing this effect appeared to be lower in the striatum than in the limbic regions. Similar results were found in the frontal cortex by measuring dopamine utilization. Moreover, tolerance developed earlier in the striatum than in the limbic areas. Possible reasons for the differential development of tolerance in the various dopamine areas investigated are proposed. 24 references. (Author abstract modified)

002145 Schaefer, Andras; Komlos, Marta; Seregi, Andras. Institute of Experimental Medicine, Hungarian Academy of Sciences, P.O. Box 67, 1450 Budapest 9, Hungary **Effects of biogenic amines and psychotropic drugs on endogenous prostaglandin biosynthesis in the rat brain homogenates.** Biochemical Pharmacology (Oxford). 27(2):213-218, 1978.

Phenylalkylamine and indolalkylamine derivatives, as well as several psychotropic drugs acting on the central nervous system, were tested for their effects on endogenous prostaglandin, (PG) biosynthesis in the rat brain homogenates. In the particulate suspension obtained by the removal of the soluble fraction from the rat brain homogenates, PG biosynthesis could be stimulated by noradrenaline, dopamine, adrenaline, serotonin, tryptamine, and to a slight extent by tyramine. Isoprenaline, DOPA, alpha-methyl noradrenaline, alpha-methyl dopamine, alpha-methyltryptamine, and 5-hydroxytryptophan were ineffective. PG biosynthesis stimulated by catecholamines or indolalkylamines responsively could be inhibited by compounds with monoamine oxidase blocking properties. In the total rat brain homogenates, another type of PG biosynthesis could be demonstrated in the absence of catecholamine or indolalkylamine that could not, or but to a slight extent, be inhibited by monoamine oxidase blocking agents. Apomorphine, oxypertine, alpha-methyl noradrenaline, promethazine, DOPA, reserpine, chlorpromazine, desipramine, yohimbine, and tetrabenazine inhibited this type of PG biosynthesis, though they failed to influence PG formation stimulated by catecholamine or idolalkylamine. A correlation could be established between the PG formation inhibitory and lipid peroxidation antagonizing effects of these compounds. Nonsteroidal antiinflammatory agents, such as indomethacin, acetylsalicylic acid, and dipyrone, inhibited both types of PG biosynthesis. The results permit the conclusion that psychotropic drugs exert their effects on endogenous PG biosynthesis in the rat brain homogenates by inhibiting various activation processes. 33 references. (Author abstract)

002146 Schechter, Martin D. Department of Pharmacology, Eastern Virginia Medical School, PO Box 1980, Norfolk, VA 23507 **Stimulus properties of d-amphetamine as compared to l-amphetamine.** European Journal of Pharmacology (Amsterdam). 47(4):461-464, 1978.

Stimulus properties of d-amphetamine and l-amphetamine were compared, a determination of the discriminable ED50 for both isomers of amphetamine was made in the same group of rats in order to calculate the potency ratio and the effect of administering both isomers together was studied to evaluate possible potentiation of effect. Rats were trained to discriminate between d-amphetamine and saline. The discriminable ED50 values for amphetamine isomers were calculated from dose response curves and the potency ratio was 4.9. Coadministration of the ED50s was shown to produce synergistic effects suggesting that the amphetamine isomers may share a common site of action. 16 references. (Author abstract modified)

002147 Schelkunov, E. L. Lab. of Psychopharmacology, Bechterev Psychoneurological Research Institute, Leningrad 193019, USSR **Efficacy of neuroleptics and antidepressants in the test of apomorphine hypothermia and some data concerning neurochemical mechanisms of the test.** Psychopharmacology (Berlin). 55(1):87-95, 1977.

In the test of apomorphine hypothermia (APH), the action of 19 imipramine-like antidepressants (IAD) and related compounds and of 13 neuroleptics on the hypothermic effect of apomorphine (AP, 5mg/kg i.p.)was investigated in mice. Strong specific neuroleptics such as trifluperidol, trifluperazine, and thioproperazine counteracted APH in doses from 0.006mg/kg, whereas IAD counteracted APH in doses from 0.25mg/kg (desmethylimipramine and melitracene). Among neuroleptics there is a good correlation between efficacy in the test of APH and efficacy in the tests of AP and amphetamine stereotypes, which reveal the central antidopamine action of neuroleptics. Among IAD there is a correlation between efficacy in the test of APH and the adrenopositive activity. The test of apomorphine hypothermia is probably the most universal simple test for the initial screening of potentially psychotropic drugs. Some previous results of the pharmacological analysis of APH are presented, which reveal the central link of APH and the central component of antagonizing APH by IAD. The hypothesis is proposed that the initial excitation of the central dopamine receptor by apomorphine leads to the activation of the noradrenergic neuron, which is the subsequent link in producing apomorphine hypothermia. 53 references. (Author abstract modified)

002148 Schmidt, M. J.; Thornberry, J. F. Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46206 **Norepinephrine-stimulated cyclic AMP accumulation in brain slices in vitro after serotonin depletion or chronic administration of selective amine reuptake inhibitors.** Archives Internationales de Pharmacodynamie et de Therapie (Ghent). 229(1):42-51, 1977.

To determine if acute or chronic alterations in availability of serotonin would alter the norepinephrine-induced elevation of cyclic-AMP in brain slices from rat limbic forebrain or brainstem a study was conducted. The research question hinged on whether the blockade of norepinephrine reuptake by desipramine (DMI) would reduce norepinephrine stimulated cyclic-AMP synthesis and a test was made of whether nisoxetine would also produce this effect. Rats were administered aqueous solutions of nisoxetine, fluoxetine, DMI, p-chloroamphetamine, or water during a light/dark cycle schedule. Cyclic-AMP accumulation was determined in vitro using slices of brain tissue and brainstem, correcting for loss during purification. The results, which replicated those in earlier studies, showed that altering serotonin availability in vivo did not influence the interaction of norepinephrine with adenylate cyclase in vitro. Neither reducing serotonin levels (p-chloroamphetamine) nor increasing availability of serotonin by blocking its reuptake (fluoxetine) affected the norepinephrine-induced elevation of cyclic-AMP in slices of the limbic forebrain of rats. But increasing norepinephrine availability by chronic administration of DMI reduced cyclic-AMP synthesis in the limbic forebrain. It was concluded as doubtful that blockade of norepinephrine reuptake alone accounted for reduction in receptor sensitivity produced by DMI since chronic administration of nisoxetine did not decrease cyclic-AMP accumulation. 27 references. (Journal abstract modified)

002149 Schorderet, M. Dept. of Pharmacology, School of Medicine, CH-1211 Geneva 4, Switzerland **Dopamine-mimetic activity of ergot derivatives, as measured by the production of cyclic AMP in isolated retinae of the rabbit.** Gerontology (Basel). 24(Supplement 1):86-93, 1978.

In a paper presented at a workshop on advances in experimental pharmacology of hydergine in Basel, December 1976, a study in which the effects of several ergot alkaloid derivatives on the concentration of cyclic adenosine monophosphate (AMP) in intact rabbit retinae investigated in vitro is reported. All components were found to be potent inducers of cyclic

AMP production. The range of effective concentrations was very well comparable with that of dopamine (or apomorphine) in the same experimental conditions. Furthermore, the accumulation of cyclic AMP induced by the ergot derivatives was blocked by fluphenazine or lithium. Both antipsychotic drugs were found to be very potent inhibitors of dopamine (or apomorphine-) induced production of cyclic AMP in the same preparation. A potential dopamine mimetic activity of ergot derivatives can be specifically tested on isolated rabbit retinae in vitro, either before undertaking experiments in vivo or in correlation with behavioral studies. 31 references. (Author abstract modified)

002150 Segal, Menahem. Isotope Department, Weizmann Institute of Science, Rehovot, Israel **The effects of SP-111, a water-soluble THC derivative, on neuronal activity in the rat brain.** Brain Research (Amsterdam). 139(2):263-275, 1978.

The effects of delta1-THC and of SP-111, a water soluble delta1-THC derivative, on spontaneous cellular activity and responsiveness to afferent stimulation were studied in the hippocampus of the awake rat. The effects of SP-111 on spontaneous and neurotransmitter induced changes in neuronal activity in anesthetized rat cerebellum and hippocampus were studied with the method of microiontophoresis. When applied parenterally into the awake rat, SP-111 caused behavioral changes similar to those seen after a delta1-THC injection. In addition, it caused a reduction of spontaneous activity of cells in the hippocampus with a single spike firing pattern without affecting firing of bursting neurons. Furthermore, the averaged evoked field responses to commissural stimulation were reduced by a third up to 2hr to 3hr after the injection. High phoretic currents of SP-111 reduced spontaneous activity of cerebellar and hippocampal neurons. Lower currents potentiated cerebellar inhibitory responses to iontophoretically applied norepinephrine. Even lower currents potentiated responses to iontophoretically applied GABA in the cerebellum. The most potent effect of SP-111 was the antagonism of aspartate-induced excitation of cells in the hippocampus. It is suggested that SP-111 antagonizes an acidic amino acid neurotransmitter in several synapses of the rat hippocampus, and that it may also potentiate the efficacy of transmission in GABAergic and noradrenergic synapses. 22 references. (Author abstract)

002151 Semenov, Ye. V.; Petrov, A. N.; Krylov, S. S. no address **/The effect of amizyl and arecoline on the activity of Na-K-ATPase and the content of Na+ and K+ in rat brain./** Vliyaniye amizila i arekolina na aktivnost' Na, K-ATF-azy i soderzhaniye ionov Na+ i K+ v golovnom mozge krys. Byulleten' Eksperimental'noy Biologii i Meditsiny (Moskva). 83(2):180-183, 1977.

The activity of Na-K-ATPase and Na+ and K+ content of rat brain were studied in response to benactyzine and arecoline. Both benactyzine and arecoline increased Na-K-ATPase activity. It is suggested this may be associated with changes in redistribution of Na+ and K+ ions in the nerve cell. Arecoline proved to cause changes in the electrolyte distribution of the depolarization type, whereas benactyzine caused changes characteristic of hyperpolarization of the nerve cell membrane. 12 references. (Journal abstract modified)

002152 Semiginovsky, B.; Jakoubek, B.; Pavlik, A.; Sobotka, P. Inst. of Pathophysiology, Medical Faculty, Charles University, Praha, Czechoslovakia **Effect of early experience, pyrithioxin and diazepam on U14C glucose utilization in rat brain during emotional stress.** Activitas Nervosa Superior (Praha). 19(4):307-309, 1977.

A summary of a paper read at the 2nd International CIANS Congress on the effect of early experience, pyrithioxin, and diazepam on (U14C) glucose utilization in rat brain during emotional stress is presented. The effect of anticipation stress on the homeostatic capacity of the brain barrier transport mechanism was examined in standard rats, rats with previous experience of painful stimulation, and rats treated with pyrithioxin. Early training increased both the general resistance to stress and the homeostatic capacity of the brain barrier system transport, while pryithioxin predominantly increased the transport capacity of the brain barrier for glucose and its metabolites. Diazepam strongly inhibited (14C) glucose transports as well as its utilization. 6 references.

002153 Shaw, J. P.; Ratcliffe, F. School of Pharmacy, Brighton Polytechnic, Brighton, BN2 4GJ, England **A lithium-carbonate-induced increase in the mouse brain 5-hydroxytryptamine metabolism.** Journal of Pharmacy and Pharmacology (London). 29(Suppl.):28p, 1977.

In a paper read at the 114th meeting of the British Pharmaceutical Conference, held at Sheffield, England, during September 1977, a lithium-carbonate-induced increase in the mouse brain 5-hydroxytryptamine (5HT) metabolism is reported. The 5HT metabolism was examined by measuring the amount of labelled 5HT recovered from mice brains up to 120 minutes after intraventricular and intravenous injection. Groups of mice had been pretreated for 3 days either with lithium carbonate or saline (i.p.,twice daily). Results suggest an increased metabolism and turnover of brain 5HT in the presence of lithium carbonate. The relationship of this finding to the clinical effects of lithium carbonate in manic-depressive psychosis is noted. 3 references.

002154 Shore, C. O.; Abraham, N.; Strahilevitz, M. Laboratory of Environmental Mutagenesis, National Institute of Environmental Health Sciences, Research Triangle Park, NC **Comparison of the effects of 5-hydroxytryptamine, dimethyltrayptamine, and 5-methoxy-N,N-dimethyltryptamine on rectal temperature in the mouse.** Research Communications in Psychology, Psychiatry and Behavior. 3(1):37-54, 1978.

Rectal temperatures were recorded and compared in C57 black mice after systemic injection of 5-hydroxytryptamine (5HT) or one of its two hallucinogenic derivatives, dimethyltryptamine, and 5-methoxy-N,N-dimethyltryptamine; and the actions of these compounds are discussed in light of a potential stimulatory effect upon central serotonergic receptors, leading to a functional spillover of 5HT. The results for the hallucinogens indicate a graduate increase toward hyperthermia with increases in dose and lipid solubility. Implications of the data for a traditional viewpoint of thermoregulation are also considered. 34 references. (Author abstract modified)

002155 Simantov, Rabi; Childers, Steven R.; Snyder, Solomon H. Department of Pharmacology, Johns Hopkins University School of Medicine, Baltimore, MD 21205 **The opiate receptor binding interactions of 3H-methionine enkephalin, an opioid peptide.** European Journal of Pharmacology (Amsterdam). 47(3):319-331, 1978.

A series of in vitro studies were undertaken to examine (3H)methionine enkephalin interactions with opiate receptor sites. (3H)Methionine enkephalin binds stereospecifically with high affinity to opiate receptors in rat brain membranes. Equilibrium experiments indicate two distinct dissociation constants with KD values of 1.8and 5.8nM respectively. (3H)Methionine enkephalin associates and dissociates from the

opiate receptor with 8 to 10 fold slower kinetics than 3H-opiates. Though several opiates have similar affinities for sites labeled by (3H)methionine enkephalin, (3H)dihydromorphine and (3H)naloxone, some opiates such as morphine, dihydromorphine and oxymorphone are only one tenth as potent in competing for (3H)methionine enkephalin as for (3H)dihydromorphine and (3H)naloxone binding. As with other opiate agonists, sodium selectively decreases the binding of (3H)methionine enkephalin. At 26 degree C, manganese but not magnesium or calcium increases the binding of (3H)methionine enkephalin, while at 0 degree C manganese decreases the binding of methionine enkephalin. 39 references. (Author abstract modified)

002156 Skolnick, Phil; Daly, John W.; Segal, David S. Laboratory of Biopsychosocial Research, NIAAA, ADAMHA, Rockville, MD 20857 **Neurochemical and behavioral effects of clonidine and related imidazolines: interaction with alpha-adrenoceptors.** European Journal of Pharmacology (Amsterdam). 47(4):451-455, 1978.

The neurochemical and behavioral effects of clonidine and related imidazolines and their interaction with alpha-adrenoceptors was examined. Clonidine and other imidazolines, including phentolamine, inhibited the norepinephrine elicited accumulation of cyclic AMP in brain slices via blockade of postsynaptic alpha-adrenoceptors. Clonidine antagonized the increase in locomotor activity induced by amphetamine in a dose dependent manner. It is suggested that the common ability of clonidine and phentolamine to antagonize norepinephrine stimulated accumulation of cyclic AMP provides a possible explanation for the similar behavioral effects of these compounds, including their antagonism of the locomotor effects of amphetamine. 13 references. (Author abstract modified)

002157 Spano, P. F.; Trabucchi, M. Institute of Pharmacology and Pharmacognosy, Univ. of Milan, Via A. Del Sarto, 21, I-20129 Milan, Italy **Interaction of ergot alkaloids with dopaminergic receptors in the rat stratum and nucleus accumbens.** Gerontology (Basel). 24(Supplement 1):106-114, 1978.

In a paper presented at a workshop on advances in experimental pharmacology of hydergine in Basel, December 1976, research is reported in which various ergot alkaloids and derivatives were investigated for their interaction with dopaminergic receptors at the level of the rat corpus striatum and nucleus accumbens. Dihydro(DH)-ergotoxine, DH-ergocornine, DH-ergocryptine, DH-ergocristine, ergotamine and DH-ergotamine were found to inhibit, at micromolar concentrations, the dopamine stimulated adenylate cyclase activity of rat striatal and nucleus accumbens homogenates. The inhibitory effect of the ergot drugs was higher in the nucleus accumbens than in the striatum. Moreover, the ergot drugs were more active in displacing 3H-haloperidol and 3H-dopamine from striatal membranes. The results, which are in apparent contradiction with previously obtained behavioral, pharmacological and clinical data, are discussed in the light of the possible presence in the central nervous system of distinct dopaminergic receptors with different conformations. 31 references. (Author abstract modified)

002158 Sparber, S. B.; Fossom, L. H. Department of Pharmacology, University of Minnesota, Minneapolis, MN 55455 **Morphine increases and d-amphetamine decreases the ratio of DOPAC:HVA in push-pull perfusate of rat caudate nucleus.** Federation Proceedings. 36(3):382, 1977.

Effects of morphine and d-amphetamine on the ratio of 3,4-dihydroxyphenylacetic acid and homovanillic acid (HVA) in rat caudate nucleus were reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Rat behavior was stabilized on a fixed-ratio 15 schedule of reinforcement for food. Perfusion of the caudate nucleus via a cannula with tritiated dopamine 30 min before sessions resulted in significant quantities of 3,4-dihydroxyphenylacetic acid and HVA being collected during performance of the operant behavior. Prior to i.p. injection and 20 min following saline, the 3,4-dihydroxyphenylacetic acid:HVA ratio approached unity and operant behavior was unaffected. Injection of morphine or d-amphetamine i.p. caused a suppression of operant behavior, morphine causing an increase in the 3,4-dihydroxyphenylacetic acid:HVA ratio and d-amphetamine causing a decrease in the ratio. Morphine thus causes a decreased release of dopamine from nerve terminals. (Journal abstract modified)

002159 Spratto, George R.; Dorio, R. Eugene. Dept. of Pharmacology & Toxicology, School of Pharmacy & Pharmacal Sciences, Purdue U., West Lafayette, IN 47907 **Effect of age on acute morphine response in the rat.** Research Communications in Chemical Pathology and Pharmacology. 19(1):23-36, 1978.

The importance of age as an experimental variable in the evaluation of the analgesic, thermic, and respiratory depressant effects of morphine was studied in male rate 1.5, 6, and 10 months of age. Significant age related responses were observed in both the analgesic and thermic responses to morphine. Also, following a dose of 30mg/kg morphine, animals 6 and 10 months of age exhibited significantly higher plasma levels of morphine, a slower decline in both plasma and brain levels of morphine, and lower brain/plasma ratios of morphine indicating possible age related changes in metabolism, excretion, and the blood-brain barrier. The dose of morphine which produced respiratory depression was significantly higher in the youngest age group; this was accompanied by higher brain levels of morphine in this group. These studies illustrate the importance of age as an experimental variable in the evaluation of drugs. 16 references. (Author abstract)

002160 Stahl, Kenneth D.; Van Bever, Willem; Janssen, Paul; Simon, Eric J. Dept. of Medicine, New York University School of Medicine, 550 First Avenue, New York, NY 10016 **Receptor affinity and pharmacological potency of a series of narcotic analgesic, anti-diarrheal and neuroleptic drugs.** European Journal of Pharmacology (Amsterdam). 46(3):199-205, 1977.

A series of 26 narcotic analgesic, antidiarrheal, and neuroleptic drugs was tested for in vitro binding to rat brain opiate receptors in the presence and absence of sodium ion and the results were correlated with assays for in vivo pharmacological potency. Highly significant correlation was found between receptor binding and analgesic potency, both in the presence and absence of sodium ion. Antidiarrheal activity was also significantly correlated with binding to brain opiate receptors in the presence of sodium. These data add support to the hypothesis that stereospecific opiate binding sites are pharmacological receptors which mediate analgesia and antidiarrheal action. Neuroleptics also were bound to opiate receptors with affinities in the micromolar range, as has been reported by others. The antidiarrheal compound loperamide exhibited no significant central opiate effects but was bound to opiate receptors from brain in vitro with high affinity. Evidence is presented suggesting that the lack of specific anal-

gesic effect is the result of poor penetration through the blood-brain barrier. The results lend further support to the similarity of opiate receptors in the brain and the intestinal tract. 23 references. (Author abstract modified)

002161 Staudacherova, D.; Mares, P.; Jilek, L.; Trojan, S. Institute of Physiology, Faculty of General Medicine, Charles University, Prague, Czechoslovakia **Ontogenetic development of pentobarbital effects on electrocorticogram in rats.** Activitas Nervosa Superior (Praha). 19(4):260, 1977.

A summary of a paper read at the 2nd CIANS Congress on ontogenetic development of pentobarbital effects on electrocorticogram (ECoG) activity in rats is presented. Pentobarbital was administred intraperitoneally in three successive doses, 10 min apart, to 55 male albino rats, aged from 5 to 90 days. In the youngest groups (5 to 7 days), pentobarbital elicited only depression of ECoG activity, whereas in 15-day-old rats, an increase in spindle frequency and signs of spindle activity in the occipital region were observed. The moment of appearance of pentobarbital evoked slow waves could be reliably determined in 18-day-old animals where slow-wave activity did not prevail in the spontaneous ECoG.

002162 Stephens, Heather R.; Nadeau, Denis; Sandborn, Edmund B. Jerry Lewis Muscle Research Centre, Dept. of Paediatrics and Neonatal Medicine, Hammersmith Hospital, Du Cane Rd., London W12 0HS, England **Absorption and distribution of sodium (2-14C)barbital in tissues of normal and dystrophic mice.** Canadian Journal of Physiology and Pharmacology (Ottawa). 56(1):76-82, 1978.

The absorption and distribution of (2-14C)barbital after oral administration was studied in various tissues, including skeletal muscle, of normal and dystrophic mice. There appeared to be a more rapid gastric emptying in the mutant homozygote as reflected in lower levels of the drug recuperated from the gastrointestinal tract. This resulted in initially higher plasma and tissue concentrations of barbital in the dystrophic mice. Two hours after oral administration, this kinetic profile was reversed so that less barbital remained in the tissues of the dystrophic mouse. The tissue/plasma concentration ratios were consistently, but not significantly, higher in all tissues of the dystrophic animals. Analysis of the half-life of the drug in both groups suggests that there is an increase in the distribution volume of barbital in the dystrophic mice. The phenomenon of more rapid absorption of the barbiturate seems to be more consistent as the symptoms of the disease progress. The altered absorption and disposition of barbital in various tissues of the dystrophic mouse support the concept that a generalized multisystemic disorder may be crucial to the pathogenesis of murine muscular dystrophy, in contradistinction to a purely myogenic origin. 26 references. (Author abstract)

002163 Strahlendorf, Jean R.; Goldstein, Frederick J.; Rossi, G. Victor; Malseed, Roger T. Philadelphia College of Pharmacy and Science, Philadelphia, PA 19104 **Differential effects of subcortical lysergic acid diethylamide and serotonin on visual cortical evoked potentials.** Federation Proceedings. 36(3):411, 1977.

The effects of LSD and serotonin on visual evoked cortical responses in immobilized, artificially ventilated cats were reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Microinjection of LSD into the dorsal raphe produced maximal increases in the first three components of the average cortical evoked potential within 5 min after injection. Serotonin depressed all three components of the cortical potential, with maximal effects occurring within 15 min after injection. In the lateral geniculate nucleus, serotonin also depressed each component of the cortical evoked potential, and LSD also depressed the visual evoked potential. Saline injection had no effect. (Journal abstract modified)

002164 Sulser, Fridolin; Vetulani, Jerzy. Dept. of Pharmacology, Vanderbilt University School of Medicine, 1501 Murfreesboro Rd., Nashville, TN 37217 **The noradrenergic cyclic AMP generating system in the limbic forebrain: a functional postsynaptic norepinephrine receptor system and its modification by drugs which either precipitate or alleviate depression.** In: Hanin, I., Animal models in psychiatry and neurology. Elmsford, N.Y., Pergamon Press, 1977. 499 p. (p. 189-198).

In a paper presented at a workshop on animal models in psychiatry and neurology held in Rockville, Maryland, in June 1977, a characterization of the noradrenergic cyclic-adenosine-3,5-monophosphate (cAMP) generating system in the rat limbic forebrain is presented. The system has several characteristics that are compatible with those of a central norepinephrine (NE) receptor system: 1) high sensitivity for agonists including NE; 2) stringent structural requirements and stereospecificity for agonists; 3) stereoselective blockade by antagonists; and 4) the ability to develop supersensitivity to agonists following reserpinization, chemical sympathectomy with 6-hydroxydopamine, or denervation of limbic forebrain structures by surgical lesioning of the medial forebrain bundle. Evidence that this system functions as a postsynaptic NE receptor system is presented. Studies of the effects of drugs which can precipitate or alleviate mental depression on the reactivity of this system have revealed that these agents cause opposite changes in reactivity. It is suggested that postsynaptic receptor mediated events may be involved in the mechanism of action of antidepressant drugs. 33 references.

002165 Touchstone, J. C.; Levin, S. S.; Novack, B.; Cooper, D. Y. University of Pennsylvania, Philadelphia, PA 19104 **Sulfates and glucuronides of parahydroxyphenobarbital in rat feces.** Federation Proceedings. 36(3):843, 1977.

A study of the metabolism of phenobarbital during its use in the induction of cytochrome P450 in rats by examining its excretion in the feces was reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. After sequential extraction and enzyme hydrolysis, thin layer chromatography was used for extraction. Following injection of tagged phenobarbital, 64% of the excreted radioactivity was identified as unconjugated p-hydroxyphenobarbital, 14% was free phenobarbital, 15% was p-hydroxyphenobarbital sulfate, and 16% was p-hydroxyphenobarbital glucuronide. The sample of feces extracted represented a portion removed from the colon 18 hr after injection of (C14)phenobarbital, and the recovered radioactivity in this fecal sample represented 11% of the injected dose. (Journal abstract modified)

002166 Tseng, Liang-Fu; Harris, R. Adron; Loh, Horace H. Department of Pharmacology, University of California, San Francisco, CA 94143 **Blockade of p-methoxyamphetamine-induced serotonergic effects by chlorimipramine.** Journal of Pharmacology and Experimental Therapeutics. 204(1):27-38, 1978.

To investigate neuronal uptake and release of 5-hydroxytryptamine (5-HT) from isolated brain tissue induced by p-methoxyamphetamine (PMA) and chlorimipramine; to determine if PMA releases 5-HT in vivo; and to test whether the 5-

HT releasing affect and other pharmacological actions of PMA can be blocked by chlorimipramine, a study was conducted. Comparison of the effects of d-p-methoxyamphetamine (d-PMA) and chlorimipramine on the uptake and release of (H)5-hydroxytryptamine ((H)5-HT) in brain tissue slices in vitro revealed that d-PMA was equipotent to chlorimipramine in inhibiting the uptake of (H)5-HT and was much more potent than chlorimipramine in increasing the release of radioactivity from slices preloaded with (H)5-HT. The results indicate that the increased release of (H)5-HT by d-PMA is not due to the inhibition of reuptake of (H)5-HT. In behavior studies, chlorimipramine reduced the disruption of fixed-ratio responding induced by d-PMA but not by d-amphetamine. In addition, the increased locomotor activity and myoclonic twitch activity of suprahyoideal muscle induced by PMA were also blocked by pretreatment with chlorimipramine. Since these behavior and pharmacological effects induced by PMA have previously been suggested to involve the serotonergic system, it is proposed that chlorimipramine blocks the effects of PMA by preventing the PMA induced release of 5-HT in the central nervous system. 24 references. (Author abstract modified)

002167 Ulus, Ismail H.; Scally, Michael C.; Wurtman, Richard J. Laboratory of Neuroendocrine Regulation, Massachusetts Institute of Technology, Cambridge, MA 02139 **Enhancement by choline of the induction of adrenal tyrosine hydroxylase by phenoxybenzamine, 6-hydroxydopamine, insulin or exposure to cold.** Journal of Pharmacology and Experimental Therapeutics. 204(3):676-682, 1978.

To examine the effects of choline on phenoxybenzamine, 6-hydroxydopamine, insulin, or cold-induced adrenal tyrosine hydroxylase activity, rats were administered choline in conjunction with each of the above treatments. Choline caused an augmentation of the adrenomedullary response to each of the treatments, but it had no apparent effect on a presynaptic enzyme, choline acetyltransferase. These observations strongly support the view that choline availability determines both the amount of acetylcholine present in nerve terminals and the amount liberated when cholinergic neurons fire. 37 references. (Author abstract modified)

002168 van Duijn, H. no address **Brain:serum and CSF:serum ratios after a single dose of dipropyl acetic acid (DPA).** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):509, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, brain, serum, and cerebrospinal fluid (CSF) ratios of dipropylacetic acid (DPA), a minor tranquilizer, after a single dose in cats are described. Samples of blood, brain, CSF, liver, bile and fat were taken from cats at different intervals after a single intravenous or subcutaneous injection of DPA. Experiments were performed under nembutal anesthesia. DPA in tissues and fluids was determined by gas chromatography. After i.v. administration of DPA a rapid penetration into brain is observed. Within 1 minute a brain:serum ratio of 0.30 is found. Interpretation of CSF levels, particularly during the first minutes, is complicated by an unknown dilution variable. However, within 10 minutes a CSF:serum ratio as high as 0.80 is established. Subcutaneous injection of DPA induced relatively high brain concentrations in an early stage (a brain:serum ratio of 0.33 after 25 minutes). In contrast to the situation after an i.v. injection, the brain:serum ratio is then, during an extensive period of time, significantly smaller. CSF DPA concentrations change in a manner much more parallel to changing serum levels than brain concentrations do. The findings after i.v. administration give strong evidence for the possibility of a direct bypass of the brain, since CSF:brain ratio is very high during the first 10 minutes after the injection. Then CSF:brain ratio stabilizes, which is compatible with a free diffusion of materials between CSF and extracellular fluid deep into the brain tissue in either direction. Apparently the protein binding of DPA in blood under these experimental circumstances is much less pronounced than in humans in steady state. This may be due to 1) occupation of binding sites (high concentrations); 2) competition between nembutal and DPA molecules for these sites; and 3) time. (Author abstract modified)

002169 van Wijk, Marijke; Meisch, Jean-Jacques; Korf, Jakob. Netherlands Institute for Brain Research, Ijdijk 28, Amsterdam, The Netherlands **Metabolism of 5-hydroxytryptamine and levels of tricyclic antidepressant drugs in rat brain after acute and chronic treatment.** Psychopharmacology (Berlin). 55(3):217-223, 1977.

Because tricyclic antidepressants (TAD) are usually given chronically to patients, both their acute and their chronic effects on 5-hydroxytryptamine (5-HT) metabolism were studied in rat brain using the probenecid method and, in addition to 5-hydroxyindoleacetic acid (5-HIAA), some other indole compounds in brain were measured. Simultaneously, TAD levels in brain and plasma were determined. Dimethylated as well as monomethylated TADs were administered, both at 10 and 25mg/kg i.p. Treatment with either 10mg/kg during 14 days or 25mg/kg given acutely resulted in a similar brain level of TAD, so any differences found could be attributed to differences in administration schedule. Drug levels in brain and plasma differed considerably after chronic and acute treatments but no major differences in the effect on 5-HIAA level in the brain were found, although accumulation of 5-HIAA following probenecid treatment was mostly lowered after treatment with dimethylated TAD. The TAD level in rat brain was not decisive for the effect on central 5-HT turnover. The monomethylated TAD affected the 5-HT turnover very little, not only acutely but also chronically. 39 references. (Author abstract)

002170 Vermeulen, N. P. E.; van Bladeren, P. J.; Breimer, D. D.; van der Gen, A. Dept. of Pharmacology, Sukfaculty of Pharmacy, University of Leiden, Wassenaarseweg 76, Leiden, The Netherlands **Hexobarbital-1′,2′-epoxide: a possible intermediate in the metabolism of hexobarbital.** Biochemical Pharmacology (Oxford). 27(1):135-138, 1978.

The identification of hexobarbital-1′,2′-epoxide in the urine of rats following intraperitoneal injection of hexobarbital is reported. The metabolic fate of the epoxide itself was studied, and 3′-hydroxyhexobarbital and 3′-ketohexobarbital were identified as the major metabolites of the epoxide. It is suggested that the epoxide pathway may be of importance in the formation of 3′-hydroxyhexobarbital and 3′-ketohexobarbital, the major metabolites of hexobarbital. 6 references.

002171 Vyskocil, Frantisek. Institute of Physiology, Czechoslovak Academy of Sciences, Budejovicka 1083, 142 20 Prague 4-Krc, Czechoslovakia **Effect of diazepam on the frog neuromuscular junction.** European Journal of Pharmacology (Amsterdam). 48(1):117-124, 1978.

Studies were conducted to determine whether diazepam influences cholinergic neuromuscular transmission, in which chloride ions play a negligible role during the release and action of acetylcholine. Diazepam had no effect on the compound action potential of frog sciatic nerve and its refractory period. At the neuromuscular junction, no changes were found

in the amplitude and frequency of miniature endplate potentials in the presence of the drug. Endplate potential amplitude and its early facilitation were unchanged. Diazepam had no effect on the amplitude of potentials evoked by ACh applied iontophoretically (0.1Hz) at low frequencies in the chemosensitive region of the postjunctional membrane. Diazepam enhanced the progressive desensitization to ACh applied at a frequency of 1Hz but did not affect recovery of sensitivity. A possible mechanism of action of diazepam at cholinergic synapses is discussed. 33 references. (Author abstract modified)

002172 Waldmeier, P. C.; Feldtrauer, J.-J.; Maitre, L. Research Department, Pharmaceuticals Division, CIBA-GEIGY Limited, Basel, Switzerland **Methylhistamine: evidence for selective deamination by MAO B in the rat brain in vivo.** Journal of Neurochemistry (Oxford). 29(5):785-790, 1977.

A new method has been developed for the separation of histamine and its metabolites after intracisternal injection of (3H)histamine into the rat brain, involving solvent extraction and subsequent thin layer chromatography. The effect of graded doses of the MAO inhibitors deprenil and pargyline, and clorgyline, on the brain levels of intracisternally injected (3H)histamine and its labelled metabolites was studied and compared to MAO A and B activity as determined with the substrates serotonin and phenethylamine, respectively. In addition, the time course of the effects of a single dose of pargyline (50mg/kg subcutaneously) was investigated. No (3H)imidazoleacetic acid could be detected in any of the control or treated animals. (3H)Histamine accounted for 9 to 12% of the total extracted radioactivity and this was not altered significantly by pretreatment with any of the MAO inhibitors up to high doses, at which both MAO A and B activities were completely inhibited. The dose response curves of the effects of deprenil and pargyline on (3H)methylimidazoleacetic acid levels were congruent with those of the MAOI effects on MAO B activity and not with those on MAO A activity. Pargyline (50mg/kg s.c.)had a long-lasting effect on the accumulation of (3H)methylhistamine and (3H)methylimidazoleacetic acid. These results suggest that methylhistamine is metabolized selectively by MAO B in rat brain. Moreover, the fact that clorgyline, at doses where phenethylamine deamination is already considerably inhibited, did not affect the deamination of methylhistamine, suggests that the latter is an even more selective substrate for MAO B than phenethylamine itself. Therefore, small doses of deprenil (0.3-3mg/kg s.c.)or pargyline (1-3mg/kg) can be used to influence histamine catabolism without interfering with catecholamine or serotonin deamination. 21 references. (Author abstract modified)

002173 Waldmeier, Peter C.; Maitre, Laurent. Research Department, Pharmaceuticals Division, Ciba-Geigy AG., Basel, Switzerland **Effects of baclofen on dopamine metabolism and interaction with neuroleptic effects.** European Journal of Pharmacology (Amsterdam). 47(2):191-200, 1978.

Effects of baclofen on dopamine metabolism and its interaction with neuroleptic effects was studied in the rat. Baclofen increased striatal levels of dopamine, homovanillic acid, and 3,4-dihydroxyphenylacetic acid (DOPAC) in a dose dependent manner at dosages above 10mg/kg. Dopamine metabolites were affected by only the (-)-isomer. The homovanillic increase after 20mg/kg was not antagonized by either scopolamine or picrotoxin. Repeated treatment with baclofen produced a smaller increase in homovanillic acid than a single administration. Baclofen reduced both the disappearance of dopamine after alpha-methyl-p-tyrosine and the acceleration of the dopamine disappearance caused by neuroleptics in the corpus striatum and the mesolimbic area. The neuroleptic-induced increases in homovanillic acid and DOPAC the DOPA accumulation after central decarboxylase inhibition were also reduced. Picrotoxin could not antagonize these effects of baclofen which, therefore, cannot be regarded as being GABAergic. It is concluded that baclofen effects on dopamine metabolism are similar to those reported by gamma-hydroxybutyric acid and are probably a consequence of inhibition of firing of dopamine neurons. 37 references.

002174 Wallenstein, M. C.; Bito, L. Z. Dept. of Pharmacology, Columbia University, College of Physicians & Surgeons, 630 W. 168th St., New York, NY 10023 **Hyperthermic effects of supracortically applied prostaglandins after systemic pretreatment with inhibitors of prostaglandin transport and synthesis.** Journal of Pharmacology and Experimental Therapeutics. 204(2):454-460, 1978.

The effect of supracortically applied prostaglandins on body temperature was studied after systemic pretreatment with inhibitors of prostaglandin transport or synthesis. Results indicate that suprafusion of 8 micrograms of either PGE1 or PGE2alpha over the visual cortex of control rabbits did not produce a statistically significant increase in body temperature. Within 1 hour, but not more than 5 to 6 hours, after systemic administration of bromcresol green (2mg/kg) or probenecid (200mg/kg), suprafusion of 8 micrograms PGE1 or PGE2alpha over the cortex produced a significant increase in body temperature. PGE1 also caused significant elevations in body temperature when suprafused over the cortex 2 to 24 hours after, but not less than 1 hour after, systemic pretreatment with paracetamol (50mg/kg) or indomethacin (10mg/kg). It is suggested that increased responsiveness in body temperature may be due either to the elimination of physiological or pharmacological antagonists or to the development of true target organ supersensitivity. 24 references.

002175 Waszczak, B. L.; Smith, C. B. Department of Pharmacology, University of Michigan Medical School, Ann Arbor, MI 48109 **Changes in mouse brain catecholamine content and tyrosine hydroxylase activity during chronic amphetamine administration.** Federation Proceedings. 36(3):406, 1977.

The effect of amphetamine on catecholamine content and tyrosine hydroxylase activity in female, albino Swiss-Webster mice was reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Mice were given d-amphetamine i.p. every 6 hr for up to 10 days, and catecholamine content and tyrosine hydroxylase activity of the hypothalamus and caudate nucleus were determined at 2 day intervals during amphetamine administration. Repeated amphetamine administration caused an initial reduction in norepinephrine and dopamine content in both brain regions. In the hypothalamus, however, both amines returned to control levels by 10 days of drug treatment, while the caudate nucleus levels of both amines were further reduced to 50% of control by 10 days. Tyrosine hydroxylase activity in homogenates increased to 140% of control in both brain areas after 10 days, but in tissue slices it remained unaffected in the hypothalamus and was reduced to 70% of control in the caudate nucleus. (Journal abstract modified)

002176 Waterfield, Angela A.; Lord, John A. H.; Hughes, John; Kosterlitz, Hans W. Unit for Research on Addictive Drugs, University of Aberdeen, Marischal College, Aberdeen AB9 1AS, Scotland **Differences in the inhibitory effects of normorphine and opioid peptides on the responses of the vasa**

deferentia of two strains of mice. European Journal of Pharmacology (Amsterdam). 47(2):249-250, 1978.

Differences in the inhibitory effects of normorphine and opioid peptides on the responses of the vasa deferentia of two strains of mice were studied. Results indicate that methionine-enkephalin and leucine-enkephalin are about 1.5times more effective in depressing the contractions of the vas deferens of Black C57/BL mice than those of white TO mice. Normorphine is much less potent on the vasa deferentia of C57/BL mice than on those of the TO mice, and inhibits the binding of (3H)-leucine-enkephalin less than that of (3H)-naltrexone. Beta-endorphin inhibits the binding of (3H)-naltrexone and (3H)-leucine-enkephalin about equally well without any strain differences. It is suggested if similar genetic differences can be found in the central nervous system, it could point a way to a new approach to the problem of heroin seeking behavior. 5 references.

002177 Wauquier, A.; Van Den Broeck, W. A. E.; Verheyen, J. L.; Janssen, P. A. J. Department of Pharmacology, Janssen Pharmaceutica, B-2340 Beerse, Belgium **Electroencephalographic study of the short-acting hypnotics etomidate and methohexital in dogs.** European Journal of Pharmacology (Amsterdam). 47(4):367-377, 1978.

Beagles, implanted with cortical and subcortical electrodes, were given etomidate i.v. (1mg/kg) over a period of 10 sec and the effects on the EEG were compared with those obtained with 7mg/kg of methohexital. Both compounds induced hypnosis for a duration of approximately 8 min. The EEGs showed a remarkable similarity. Visual inspection of the records as well as power spectrum analysis revealed a sustained omega activity with underlying fast activity. The configuration of the waves was rather sharp. The power obtained after etomidate was, however, two to three times that obtained after methohexital. When the animals awoke from etomidate-induced hypnosis slow-waves appeared and were followed by alpha activity, whereas after methohexital hypnosis beta activity predominated. Etomidate slightly increased heartrate, but respiratory depression was not observed. Methohexital caused pronounced tachycardia and apnea. In three out of six dogs methohexital caused myoclonus of the hind legs upon awakening from anesthesia. Etomidate induced myoclonus in one dog during hypnosis. 22 references. (Author abstract)

002178 Weinstein, Harel; Johnson, Carl L.; Green, Jack P. Mount Sinai School of Medicine, New York, NY 10029 **Molecular determinants for the action of tryptamines on an LSD receptor.** Federation Proceedings. 36(3):290, 1977.

Actions of tryptamines on stomach contraction and on high affinity binding of LSD by brain membranes in the rat will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. The potencies of tryptamine in contracting the stomach correlated with potencies in inhibiting LSD binding, suggesting similar receptors. Biological potency was related to electron charge distribution, electrostatic potential fields around the molecules, force vectors for optimal drug receptor orientation, and localization of molecular sites most susceptible to polarization in drug receptor complexes. Potency was correlated with frontier electron densities at specific atoms, which follows the localization of electron density in the highest occupied molecular orbital of serotonin. The change in pharmacological potency with indole ring substitution comes from different density distributions in the highest occupied molecular orbital. (Journal abstract modified)

002179 Weinstock, Marta; Thoa, Nguyen B.; Kopin, Irwin J. Department of Pharmacology, Hebrew University School of Medicine, Hadassah Hospital, Jerusalem, Israel **Beta-adrenoceptors modulate noradrenaline release from axonal sprouts in cultured rat superior cervical ganglia.** European Journal of Pharmacology (Amsterdam). 47(3):297-302, 1978.

Superior cervical ganglia of rats grown in organ culture were used to study the effect of beta-receptor stimulants and antagonists on (3H)noradrenaline release in response to stimulation by KCl. (-)-Isoprenaline increased by 20 to 25% the release ot (3H)noradrenaline from cultured ganglia exposed to KCl. Isoprenaline did not modify either the spontaneous (noncalcium dependent) release of (3H)noradrenaline from cultured ganglia, or the KCl stimulated release from fresh ganglia. The effect of (-)-isoprenaline was blocked by (-)-propranolol and by butoxamine, but not by (+)-propranolol, practolol, or sotalol. Isoprenaline induced augmentation of (3H)noradrenaline release and its antagonism by (-)-propranolol still occurred in the presence of desmethylimipramine. It is suggested that presynaptic beta-receptors in sympathetic nerve terminals may be involved in a positive feedback of noradrenaline release. 13 references. (Author abstract)

002180 Winter, J. C. Dept. of Pharmacology & Therapeutics, School of Medicine, 127 Farber Hall, SUNY, Buffalo, NY 14214 **Stimulus properties of phenethylamine hallucinogens and lysergic acid diethylamide: the role of 5-hydroxytryptamine.** Journal of Pharmacology and Experimental Therapeutics. 204(2):416-423, 1978.

Effects upon mescaline mediated stimulus control of BC-105 and cinanserin, two different antagonists of 5-hydroxytryptamine, and of p-chlorophenylalanine were examined in rats. In subjects treated with one of the antagonists before administration of mescaline, the degree of antagonism was positively correlated with the dose of antagonist. In contrast, pretreatment with p-chlorophenylalanine (150 or 300mg/kg) failed to produce significant effects. An indication of the specificity of action of BC-105 was provided by its failure, over a range of doses, to antagonize the stimulus of d-amphetamine. Doses of LSD, 2,5-dimethoxy-4-methylamphetamine and 2,5-dimethoxy-4-ethylamphetamine, which mimicked mescaline in mescaline treated rats, were blocked by the same doses of either BC-105 or cinanserin found to be effective against mescaline. These data suggest that a serotonergic mechanism plays a significant role in stimulus-control-induced mescaline. Drugs which mimic mescaline, whether they be of indoleamine or phenethylamine class, appear to do so via the same mechanism. 61 references.

002181 Wolf, P.; Haas, H. L. Neurochirurgische Universitatsklinik, CH-8091 Zurich, Switzerland **Effects of diazepines and barbiturates on hippocampal recurrent inhibition.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 299(3):211-218, 1977.

The effects of two diazepines (diazepam and Ro-11-7800) and three barbiturates (thiamylal, pentobarbital, phenobarbital) on gamma-aminobutyric acid (GABA) mediated recurrent inhibition were assessed on single rat hippocampal pyramidal cells and on population spikes using extracellular recording techniques. Recurrent inhibition was evoked in spontaneously active CA1 pyramidal cells by stimulation of the fimbria or the alveus with single shocks. Microiontophoretic application of Ro-11-7800 or systemic application of diazepines or barbiturates resulted in an increase of the duration of the inhibition and in a concomitant depression of the spontaneous firing in most neurones tested. When the firing rates were kept con-

stant artificially, using excitant amino acids, a prolongation of the recurrent inhibition was observed with barbiturates but not with diazepines. The duration of the inhibition, which was assessed from CA1 population spikes elicited by double shocks to the fimbria, was prolonged following systemic application of diazepines or barbiturates. It is concluded that both diazepines and barbiturates are able to potentiate GABAergic recurrent inhibition in the hippocampus. 38 references. (Author abstract modified)

002182 Wolfe, G. W.; Bousquet, W. F.; Schnell, R. C. Department of Pharmacology and Toxicology, School of Pharmacy, Purdue University, West Lafayette, IN 47907 **Circadian variations in response to amphetamine and chlorpromazine in the rat.** Federation Proceedings. 36(3):423, 1977.

Circadian variations in response to d-amphetamine and chlorpromazine in rats were reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. d-Amphetamine altered locomotor activity, with peaks occurring at 4 PM and 4 AM and nadirs occurring at 12 N and 8 PM, but brain and plasma amphetamine levels at these times did not differ. Chlorpromazine caused a circadian variation in hypothermia, with the greatest decrease in body temperature occuring at 12 N; brain and plasma levels of chlorpromazine disposition did not vary at different times of the day. Thus, the temporal variations in locomotor activity and temperature occurring in response to these drugs may reflect time dependent changes in tissue sensitivity to the drugs. (Journal abstract modified)

002183 Wong, Chak-lam; Bentley, Geoffrey A. Department of Pharmacology, Monash University, Clayton, Victoria 3168, Australia **Increased antagonist potency of naloxone caused by morphine pretreatment in mice.** European Journal of Pharmacology (Amsterdam). 47(4):415-422, 1978.

An attempt to determine whether an increase in the potency of naloxone in mice pretreated with morphine is due entirely to the amount of morphine used, or is related directly to the antinociceptive effect of morphine is described. Using the writhing test in mice, it was shown that pretreatment with a single dose of morphine hydrochloride given 3 h previously caused a marked increase in the antagonistic effect of naloxone without any change in the antinociceptive action of morphine itself. When mice were pretreated with different doses of either morphine alone, or in combination with naloxone, so that each treatment produced the same antinociceptive effect, the increase in naloxone potency was proportional only to the antinociceptive effect of the pretreatment and not to the total dose of morphine present. It was also found that the concurrent administration of naloxone plus morphine prevented the development of acute dependence to morphine, as measured by the jumping reaction after challenge with naloxone. 12 references. (Author abstract modified)

002184 Wurtman, Judith J.; Wurtman, Richard J. Dept. of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, MA 02138 **Fenfluramine and fluoxetine spare protein consumption while suppressing caloric intake by rats.** Science. 198(4322):1178-1180, 1977.

The effects of fenfluramine and other anorectic drugs on the consumption of both protein and total calories by rats given simultaneous access to two isocaloric diets containing 5 or 45 percent casein were examined. Anorectic doses of fenfluramine failed to decrease protein intake but increased the proportion of total dietary calories represented by protein. In contrast, anorectic doses of d-amphetamine decreased protein and calorie consumption proportionately. Subanorectic doses of fenfluramine also increased the proportion of caloric intake represented by protein among animals given prior treatment with the serotonin precursor tryptophan. Fluoxetine, a drug that blocks reuptake of serotonin, similarly spared protein consumption while reducing caloric intake. These observations indicate that two distinct brain mechanisms, sensitive to different drugs, underlie the elective consumption of protein and calories. 13 references. (Journal abstract)

002185 Yarbrough, George G. Merck Institute for Therapeutic Research, West Point, PA 19486 **Studies on the neuropharmacology of thyrotropin releasing hormone (TRH) and a new TRH analog.** European Journal of Pharmacology (Amsterdam). 48(1):19-27, 1978.

Thyrotropin releasing hormone (TRH) and a new TRH analog (all L-pyro-2-aminoadipyl-histidyl-thiazolidine-4-carboxamide, MK-771) were compared with several other peptides for their analeptic activity and their ability to enhance the excitatory actions of microiontophoretically applied acetylcholine (ACh) on cerebral cortical neurons of rats. TRH and MK-771 offset the narcosis induced by pentobarbital in mice, whereas the C-terminal free acid derived from TRH, melanostatin, somatostatin and pyroglutamyl-histidineamide were found inactive. Similarly, of these peptides only TRH and MK-771 induced a tremor of the forepaws in pentobarbital anesthetized mice. Employing comparable ejection currents and durations, only TRH and MK-771, applied by microiontophoresis, enhanced the excitatory actions of ACh on spontaneously active cortical neurons in anesthetized rats. Based on these findings and other recent data, it is suggested that the interactions of TRH and MK-771 with cholinergic mechanisms may underlie some of the actions, including their antianesthetic effects, of these peptides. 26 references. (Author abstract)

002186 York, James L.; Maynert, E. W. New York State Research Institute on Alcoholism, 1021 Main St., Buffalo, NY 14203 **Alterations in morphine analgesia produced by chronic deficits of brain catecholamines or serotonin: role of analgesimetric procedure.** Psychopharmacology (Berlin). 56(2):119-125, 1978.

The responsiveness of rats to nociceptive stimuli was determined using both the radiant heat tail flick procedure and electrical stimulation of the trigeminal nerve sufficient to induce a squeal. Depletion of forebrain serotonin (produced by surgical lesions of the dorsal and medial raphe nuclei) or of catecholamines (produced by intracerebral injections of 6-hydroxydopamine) did not affect tail flick latency. Squeal thresholds, however, were elevated nearly 300% over controls in the serotonin deficient animals and reduced by over 50% in the catecholamine deficient animals. The effect of morphine on the tail flick latency did not differ in the lesioned and control rats. In the squeal procedure, however, the normal elevation in threshold produced by morphine was attenuated in the raphe lesioned rats and was markedly enhanced in the animals treated with 6-hydroxydopamine. These findings are discussed in view of the fact that the squeal procedure differs from conventional analgesimetric procedures in both the severity of nociceptive stimulation and the extent of spinal cord involvement. The observation that morphine analgesia was unimpaired after treatment with 6-hydroxydopamine but was diminished in raphe lesioned rats suggests that the elevation in squeal threshold normally produced by morphine may be mediated through impairment of serotonergic function. 46 references. (Author abstract)

002187 Ziance, R. J. Department of Pharmacology, University of Georgia School of Pharmacy, Athens, GA 30602 **Effect of beta adrenergic receptor antagonists on d-amphetamine and potassium-induced release of 3H-norepinephrine from rat brain in vitro.** Federation Proceedings. 36(3):382, 1977.

A paper presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977, reports effects of beta-adrenergic receptor antagonists on d-amphetamine and potassium-induced release of tritiated norepinephrine from rat brain. Chopped cerebral cortex tissue from rat was incubated with tritiated norepinephrine, after which d-amphetamine was added, causing a release of norepinephrine. Addition of sotolol or propranolol prior to amphetamine reduced the amphetamine-induced release of norepinephrine. Addition of 1 microMole propranolol attenuated the effects of 0.5microMole d-amphetamine. Incubation of tissue with tritiated norepinephrine and potassium increased the release of norepinephrine; this effect of potassium was not altered by beta-adrenergic antagonists. It is concluded the attenuating effect of beta-adrenergic receptor antagonists may be related in part to their ability to increase the deaminated catabolism of tritiated norepinephrine. (Journal abstract modified)

04 MECHANISM OF ACTION: BEHAVIORAL

002188 Aigner, Thomas Gale. Virginia Commonwealth University/Medical College of Virginia **Studies of the reinforcing properties of intravenously self-administered compounds in rhesus monkeys. (Ph.D. dissertation).** Dissertation Abstracts International. Ann Arbor, MI, Univ. M-films, No. 77-20966 HC$15.00 MF$8.50 163 p.

Three experimental procedures were used to study the reinforcing properties of intravenously self-administered compounds in rhesus monkeys. In the rapid substitution procedure, 16 psychoactive compounds were tested for their ability to maintain a conditioned response when substituted in a sequence of cocaine hydrochloride, saline, cocaine, and a test compound. It was found that morphine, oxymorphone, codeine, pentazocine, methylphenidate, and d-amphetamine maintained responding at rates greater than for saline. Naloxone, cyclazocine, levallorphan, scopolamine, chlorpromazine, fenfluramine, and (+)-9-nor-alpha-hydroxy-hexa-hydrocannabinol failed to support responding. In the 6 day self-administration procedure, neither nalorphine nor scopolamine maintained self-administration behavior at greater rates than for saline. In the food/drug choice procedure, drugs were ranked according to their capacity to compete with food reinforcement. In order of decreasing efficacy, reinforcers were morphine, pentazocine, nalorphine, and cyclazocine, the last being no more effective than saline. It is concluded that the rapid substitution procedure in combination with the food/drug choice procedure can yield both qualitative and quantitative data regarding drug reinforcers. (Journal abstract modified)

002189 Alpern, Herbert P.; Jackson, Stanley J. Dept. of Psychology, University of Colorado, Boulder, CO 80309 **Short-term memory: a neuropharmacologically distinct process.** Behavioral Biology. 22(2):133-146, 1978.

To determine whether cholinergic, dopaminergic, noradrenergic, and/or serotonergic synaptic activity is necessary for the expression of short-term memory (STM) in mice, male mice of the C57BL/6IBG strain, trained to develop a successive reversal learning set, were delayed response tested at an interval where STM has been previously shown to be quite strong. When treated with atropine or scopolamine, behavior was impaired; however, neither diethyldithiocarbamate, sotalol, propranolol, phentolamine, haloperidol, nor p-chlorophenylalanine reliably altered delayed responding. Since all of the synaptic systems studied have been implicated in the expression of long-term memory and consolidation processes, the findings of this study indicate that STM involves more delimited neurohumoral substrates, and suggest that STM is morphologically distinct from other memory systems. 44 references. (Author abstract)

002190 Anderson, Janis L.; Leith, Nancy J.; Barrett, Robert J. Department of Psychology, Vanderbilt University, Nashville, TN 37213 **Tolerance to amphetamine's facilitation of self-stimulation responding: anatomical specificity.** Brain Research (Amsterdam). 145(1):37-48, 1978.

To test for possible anatomical specificity of electrode placement in the development of tolerance to amphetamine facilitation of self-stimulation responding, 37 Fisher or Harlan rats were trained to bar-press for hypothalamic stimulation (60 Hz, AC). Following several sessions during which small doses of D-amphetamine were administered to demonstrate facilitation, the subjects were placed on a 4 day D-amphetamine regimen. During this time they were given three daily injections of continuously increasing doses of D-amphetamine (total 78mg/kg). Subsequent tolerance was shown for electrodes stimulating dorsal or medial hypothalamic structures (H2 field of Forel, dorsal medial forebrain bundle, medial hypothalamic nuclei), but did not develop with ventral or lateral hypothalamic stimulation sites (fornix, ventral medial forebrain bundle). Results clearly demonstrate that the development of tolerance is dependent on the location of the stimulating electrode. 28 references. (Author abstract modified)

002191 Appel, James B.; Kuhn, Donald M.; White, Francis J. Behavioral Pharmacology Laboratory, Department of Psychology, University of South Carolina, Columbia, SC **Dual receptor mediation of the discriminative stimulus properties of pentazocine.** In. Ho, B., Drug Discrimination and State Dependent Learning. New York, Academic Press, 1978. 392 p. (p. 149-162).

Studies in rats on the discriminative stimulus properties of pentazocine, a drug with mixed narcotic agonist/antagonist properties, are reviewed with emphasis on studies attempting to specify the precise neurochemical nature of the pentazocine cue. Examination of the effects of pentazocine on rats trained under various schedules of operant responding and of the effects of naltrexone and haloperidol on pentazocine cued responding revealed that the discriminative stimulus effect of pentazocine is mediated by two sets of receptors. Partial blockade of the pentazocine effect was produced by naltrexone and haloperidol, suggesting the direct involvement of narcotic receptors and the indirect involvement of dopamine receptors. It was also found that the discriminative properties of pentazocine reside completely within the levorotatory isomer. It is suggested that, since the psychotomimetic properties of the drug in humans appear to be associated exclusively with the dextrorotatory isomer, the discriminative stimulus properties of pentazocine in rats do not reflect its psychotomimetic properties in humans. It is also suggested that since cyclazocine and levallorphan which have discriminative stimulus properties similar to those of pentazocine are not known to produce physical dependence, the stimulus properties of pentazocine are probably not related to its addictive properties. 37 references.

002192 Arushanian, Edward B.; Avakian, Ruben M. Medical Institute, Chita, USSR **Metrazol-induced petit mal: the role played by monoaminergic mechanisms and striatum.** Pharmacology Biochemistry and Behavior. 8(2):113-117, 1978.

To study the role of monoaminergic transmission mechanisms and striatum in seizures evoked by subconvulsive doses of metrazol, monoaminergic drugs (including apomorphine, 5-hydroxytryptophan, and chlorpromazine) were administered to rats prior to injection of metrazol in gradually increased doses. Gradually accumulating subconvulsive doses of metrazol gave rise to behavioral and electrographic effects close to petit mal epilepsy: slow negative waves and spike wave complexes on EEG, frozen and myoclonic jerks. Intensification of monoaminergic transmission with apomorphine, DOPA or 5-hydroxytryptophan attentuated, but inhibition (chlorpromazine, haloperidol and p-chlorphenylalanine), on the contrary, increases the subconvulsive effect of metrazol. Low frequency stimulation of the striatum potentiated, and lesion limited expressiveness of metrazol induced petit mal, while bilateral electrolytic lesion of the striatum eliminated apomorphine, DOPA and haloperidol action, but slightly changes the effects of chlorpromazine, 5-hydroxytrptophan and p-chlorphenylalanine. It is claimed that pharmacological modulation of the monoaminergic transmission can be useful for clinical treatment of petit mal epilepsy. 17 references. (Author abstract modified)

002193 Baile, Clifton A.; McLaughlin, Carol L. University of Pennsylvania School of Veterinary Medicine, Kennett Square, PA 19348 **Feeding behavior of sheep following intravenous injection of imidazo benzodiazepines.** Federation Proceedings. 36(3):460, 1977.

Effects of three imidazo benzodiazepines (U-38,335, U-38,043, U-39,219) on feeding behavior of sheep were reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Sheep were injected with 0, 2, 8, or 16mg of the drugs. The three drugs all caused intense feeding activity. Total activity and taxis were unchanged. The feeding behavior responses were similar to those produced by elfazepam. Drinking time also increased and water drunk per unit of feed increased seven-fold. U-39,219 elicited more water intake than the other benzodiazepines. 1 reference. (Journal abstract modified)

002194 Balzamo, E.; Vuillon-Cacciuttolo, G. Equipe d'ecophysiologie des etats de vigilance chez les primates, Bould. Jean Moulin, F-13385 Marseilles Cedex 4, France **/Sleep changes induced by chronic administration of S-1694 (Survector)./** Etude chez le singe rhesus des modifications du sommeil induites par le S.1694 en administration prolongee. Psychopharmacology (Berlin). 55(3):225-231, 1977.

To investigate sleep changes induced by chronic administration of S-1694 (Survector), five adult Macaca mulatta were studied during chronic administration (24 days) of S-1694 (10mg/kg, i.m.). This substance induced a significant increase of the first awakening (delaying sleep onset) and an enhancement of the duration of REM and stage 4 sleep. After withdrawal, the waking effect disappeared, but the increase in stage 4 sleep was maintained for 1 week and REM enhancement kept rising for 15 days. This observation of long-term action is seen to underline the validity of drug experiments in chronic treatment: S-1694 might set a new type of monoaminergic systems regulation. 12 references. (Journal abstract modified)

002195 Barry, Herbert III; Krimmer, Edward C. Department of Pharmacology, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA **Pharmacology of discriminative drug stimuli.** In: Ho, B., Drug Discrimination and State Dependent Learning. New York, Academic Press, 1978. 392 p. (p. 3-32).

Studies in animals (including rats and dogs) pertaining to the use of drugs as discriminative stimuli are reviewed. The pharmacological characteristics of discriminative drug stimuli and related attributes, such as dissociative, punitive, rewarding or reinforcing effects are summarized. Evidence is presented that a change in central nervous system function is necessary for the discriminative drug stimulus to occur. Methodological considerations including training techniques, drug dosages, and time intervals between drug administration and testing are discussed. Studies of the degree to which a drug discrimination response is specific to that drug or generalizes to other drugs are also discussed. Several categories of drugs which may be differentiated from each other on the basis of the studies reviewed include: 1) sedatives and minor tranquilizers (including barbiturates, alcohol and benzodiazepines); 2) narcotic analgesics; 3) major tranquilizers (phenothiazines); 4) muscarinic cholinergic agonists; 5) nicotinic cholinergic agonists; 6) hallucinogens (mescaline, lysergic acid diethylamide; 7) cannabinoids; and 8) stimulants (amphetamines, methylphenidate and cocaine). 88 references.

002196 Bhargava, Hemendra N. Dept. of Pharmacognosy and Pharmacology, University of Illinois at the Medical Center, Chicago, IL 60612 **Time course of the effects of naturally occurring cannabinoids on morphine abstinence syndrome.** Pharmacology Biochemistry and Behavior. 8(1):7-11, 1978.

The effects of a single intraperitoneal injection of (10mg/kg) of delta9-tetrahydrocannabinol, delta8-tetrahydrocannabinol and 11-hydroxy-delta8-tetrahydrocannabinol on abstinence syndrome were investigated in mice rendered dependent on morphine by pellet implantation. In morphine dependent mice from which the pellets had been removed, delta9-tetrahydrocannabinol inhibited the naloxone precipitated jumping response as being produced between 2 to 4 hr after delta9-tetrahydrocannabinol administration. Similarly, in mice from which pellets were not removed, delta9-tetrahydrocannabinol suppressed the jumping response; however, the intensity of effect was less than when the pellets were removed. Delta8-tetrahydrocannabinol and 11-hydroxy-delta8-tetrahydrocannabinol were not effective in suppressing morphine abstinence syndrome 2 hr following their administration. The suppression of jumping response was specific, since, the vertical jumping behavior induced by coadministration of amphetamine and L-dopa was not affected by cannabinoids. These results demonstrate that single injection of delta9-tetrahydrocannabinol is effective in controlling morphine abstinence syndrome for 24 hr, and that the drugs related to cannabinoids may show promise in narcotic detoxification. 22 references. (Author abstract)

002197 Boismare, F.; Le Poncin, M.; Lefrancois, J. Dept. de Pharmacologie, Hotel Dieu, rue de Lecat, F-76036 Rouen, France **/Memorization and central catecholamines after a craniocervical injury carried out in rats: influence of imipramine administration./** Memorisation et catecholamines centrales apres un traumatisme cranio-cervical experimental chez le rat: influence d'une administration d'imipramine. Psychopharmacology (Berlin). 55(3):251-256, 1977.

A study was conducted of the effects of imipramine on memorization and central catecholamines in rats who received a craniocervical injury. The injury was carried out so that rats received whiplash without coma. Two days after the whiplash

rats showed disturbed acquisition of a labyrinth behavior which persisted at least 7 days. Disturbance of retention was not observed when the acquisition was performed before the injury. Treatment with 1mg/kg imipramine after the whiplash removed behavioral effects and biochemical disturbances. Results agree with clinical observations, and a possible causal relation is hypothesized between the disturbance of learning behavior and the decrease of cerebral levels of noradrenaline induced by the whiplash. 11 references. (Journal abstract modified)

002198 Boisse, Norman R.; Okamoto, Michiko. Dept. of Medicinal Chemistry and Pharmacology, College of Pharmacy, Northeastern University, Boston, MA 02115 **Physical dependence to barbital compared to pentobarbital. IV. Influence of elimination kinetics.** Journal of Pharmacology and Experimental Therapeutics. 204(3):526-540, 1978.

To examine the influence of elimination kinetics in the differing withdrawal characteristics previously found using a chronically equivalent dosing method in cats, the rates of elimination for barbital and pentobarbital were adjusted to mimic each other. The rate of barbiturate elimination after chronically equivalent pentobarbital dosing was reduced by barbital substitution or by first-order pentobarbital dose reduction, with the result that withdrawal signs became mild and appeared later (3 days postdrug). The rate of barbiturate elimination after chronically equivalent barbital dosing was increased by pentobarbital substitution or by peritoneal dialysis of barbital, with the result that withdrawal signs became severe and appeared sooner (within 1 day). These findings conclusively support the key role of the rate of barbiturate elimination to expose underlying physical dependence to barbiturates. Furthermore, physical dependence and its expression in withdrawal must be regarded separately to evaluate and compare critically the dependence capability of different drugs. 15 references. (Author abstract modified)

002199 Boisse, Norman R.; Okamoto, Michiko. Department of Medicinal Chemistry and Pharmacology, School of Pharmacy, Northeastern University, Boston, MA 02115 **Physical dependence to barbital compared to pentobarbital. III. Withdrawal characteristics.** Journal of Pharmacology and Experimental Therapeutics. 204(3):514-525, 1978.

To characterize comparative withdrawal characteristics in cats after chronically equivalent barbital and pentobarbital dosing for 5 weeks, treatments were abruptly stopped and the animals were carefully observed for signs of barbiturate withdrawal. The severity of withdrawal was assessed at preset times by counting the number of grand mal type convulsions and subjectively rating 20 additional motor, autonomic and behavioral signs including tremors, twitches, myoclonic jerks, postural disturbances and motor incoordination. Ratings achieved at peak intensity (raw scores) and their incidences were used to compute total intensity scores for each graded sign. For all quantitative measures, withdrawal signs were less severe for barbital than for pentobarbital, with strikingly lower incidences of convulsions, bizarre (hallucinatory) behavior and death. The withdrawal signs for barbital appeared later, developed more slowly and persisted longer than those for pentobarbital. That the onset and then peak of withdrawal signs occurred when the extents of decline from peak blood concentration of barbital and pentobarbital were similar suggests that the time course of withdrawal might be inversely related to residual concentrations of drug, i.e. negative dose response. 58 references. (Author abstract modified)

002200 Boissier, J. R.; Oberlander, C.; Dumont, C.; Peterfalvi, M. Centre de Recherches Roussel-Uclaf, B.P. 9, F-93230 Romainville, France **Pharmacological interactions with circling behaviour induced by the piperidinyl indole derivative RU 23686.** Psychopharmacology (Berlin). 55(1):53-60, 1977.

Circling behavior in rats induced by RU-23686 (5-methoxy 3-(4-piperidinyl) 1H-indole hydrochloride) was studied as regards pharmacological interactions with psychotropic compounds and the effects of 6-hydroxydopamine (6-OHDA) lesions on circling behavior. In striatal or 6-OHDA lesioned rats, alphamethyl p-tyrosine (alphaMT) did not modify contralateral (C) turns, while in the latter case only ipsilateral (I) turns were decreased. FLA-63, propranolol, and desipramine were also inactive in rats with a unilateral striatal lesion. Haloperidol reduced the effects of a 10mg/kg dose of RU-23686 in striatal lesioned rats but was without effect against a dose of 20mg/kg; in 6-OHDA lesioned rats, haloperidol blocked induced I turns but either did not affect or increased C turns. Phenoxybenzamine and p-chlorophenylalanine (PCPA) reduced the effect of RU-23686 in rats with a striatal lesion. It is concluded that ipsilateral circling, which is blocked by haloperidol and alphaMT, could be related to a presynaptic action causing dopamine release. On the other hand, C turns do not depend on apomorphine sensitive dopamine receptors in the striatum. A minor or indirect role of 5-hydroxytryptamine (5-HT) containing areas is suggested from the response to PCPA and the lack of effect of other drugs interfering with 5-HT. Results obtained from interactions with phenoxybenzamine, caffeine, and reserpine and the bimodal response to RU-23686 observed in 6-OHDA lesioned rats could indicate an interference with adrenergic processes. 26 references. (Author abstract modified)

002201 Boulu, Roger G. Dept. of Pharmacology, Faculte de Sciences pharmaceutiques et biologiques, F-75006 Paris, France **Effect of dihydroergotoxine on thalamic- and pyramidal-evoked responses in the cat under transient ischemia.** Gerontology (Basel). 24(Supplement 1):139-148, 1978.

In a paper presented at a workshop on advances in the experimental pharmacology of hydergine in Basel, December 1976, a study on the effect of dihydroergotoxine on thalamic and pyramidal evoked responses in cats under transient schemia is described. Iterative transient cerebral ischemic aggressions were produced by interrupting the blood flow in both common carotid arteries for 2 min in unanesthetized cats whose basilar artery has been permanently ligated. The influence of ischemia upon cerebral cortex was assessed by recording electrocortical activity (ECoG) indirect pyramidal tract response (I) and thalamic evoked potentials induced by electrical stimulation of the contralateral forelimb. In control animals, the repetition of ischemic episodes delayed the recovery of the indirect pyramidal tract response, demonstrating an impairment of cortical excitability. Otherwise, cerebral ischemia induced an increase of thalamic evoked responses. This phenomenon appears to result from the suppression of inhibitory corticofugal influence. DHET did not significantly modify the disappearance times of the ECoG and of the I corticopyramidal response or the recovery delay of the ECoG, but it improved the recovery time of I and inhibited the ischemic increase of the thalamic evoked potential (0.3and 0.6mg/kg). These results suggest that DHET exerts a protective effect on the ischemic cerebral cortex in the experimental conditions used. 16 references. (Author abstract modified)

002202 Broitman, Susana T.; Donoso, A. O. Instituto de Investigaciones Cerebrales, Facultad de Ciencias Medicas,

Universidad Nacional de Cuyo, Mendoza, Argentina **Effects of chronic imipramine and clomipramine oral administration on maternal behavior and litter development.** Psychopharmacology (Berlin). 56(1):93-101, 1978.

To examine the effects of chronic imipramine (IM) and clomipramine (CIM) on maternal behavior and litter development, IM or CIM was orally administered to female rats either before pregnancy or during nursing. IM caused a significant decrease of bodyweight in both groups of animals and affected the bodyweight of litters when administered during nursing. CIM reduced the increase of weight in the mothers throughout the experiment. Both IM and CIM decreased water and food intake and locomotor activity of the adult rats. Rats treated during nursing with IM showed decreased maternal behavior at various times of treatment. The milk intake of pups from drug treated mothers also decreased. Pup eye opening was delayed by CIM both before pregnancy and during nursing and by IM treatment during nursing. Vaginal opening was retarded in female litters from mothers treated during nursing. Open-field behavior showed modifications at 60 days of age in male pups from mothers exposed to IM during nursing. Results indicate that the two tricyclic drugs are able to produce general and behavioral modifications in both mothers and their litters. These modifications seem to depend on whether the drug is given before pregnancy or during nursing. Control experiments in dams fed with a restricted diet suggest that the observed alterations in maternal behavior and litter development are not due to the undernourishment caused by drug administration. 33 references. (Author abstract modified)

002203 Brus, Ryszard; Herman, Zbiegniew S.; Jamrozik, Zofia. Zaklad Farmakologii Instytutu Biologiczno-Fizjologicznego S1. AM, 38 Marksa, Zabrze 41-808, Poland **Behavioral effects of apomorphine during development of rats.** Acta Physiologica Polonica (Warszawa). 28(3):243-246, 1977.

The behavioral effects of apomorphine in a dose of 1.5mg/kg i.p. were studied in 1121 male Wister rats at the age of 3, 4, 6 weeks and 3, 5, 6 months. Behavioral features typical for apomorphine were observed in rats from the sixth week of life. It is concluded that maturation of central dopaminergic receptors in rats occurs at about the sixth week of life. 12 references. (Journal abstract modified)

002204 Burov, Yu. V.; Speranskaya, N. P. Laboratoriya po izyskaniyu i izucheniyu sredstv dlya profilaktiki i lecheniya narkomaniy, Institut farmakologii AMN SSSR, Moscow, USSR **/Effect of psychotropic drugs on the development of defense conditioned reflex during experimental neurosis./** Vliyaniye psikhtropnykh veshchestv na vyrabotku oboronitel'nogo uslovnogo refleksa eksperimental'nom nevroze. Byulleten' Eksperimental'noy Biologii i Meditsiny (Moskva). 83(6):696-698, 1977.

A study of the effects of psychotropic agents with tranquilizing action on one form of experimental neurosis in the rat is reported. Experimental neurosis was induced in rats through long-term exposure to the negative emotional factor of a neighboring rat's reaction to pain, resulting in alteration of development of motor defense conditioned reflex. Benactyzine, diazepam, chlordiazepoxide, and sodium hydryxybutyrate improved the formation of defense conditioned reflex during this form of neurosis. Trioxazine, trifluoperazine, and amphetamine produced no such effect. It is suggested the experimental neurosis model may be used in other tests of the tranquilizing action of psychotropic drugs. 11 references. (Journal abstract modified)

002205 Buus Lassen, Jorgen. Dept. of Pharmacology, A/S Ferrosan, Sydmarken 1-5, DK-2860 Soeborg, Denmark **Piperoxane reduces the effects of clonidine on aggression in mice and on noradrenaline dependent hypermotility in rats.** European Journal of Pharmacology (Amsterdam). 47(1):45-49, 1978.

Aggression in isolated male mice and hypermotility in rats produced by the noradrenaline releaser H-77/77 were studied after subcutaneous administration of the alpha-adrenergic agonist clonidine and the alpha-antagonist piperoxane. Results indicate that clonidine (0.0005 to 0.5mg/kg) inhibited both behaviors, while piperoxane showed a weak and short-lasting antiaggressive effect and no H-77/77 antagonism. Inactive doses of piperoxane reduced the inhibitory effects of clonidine. These findings suggest that isolated induced aggression in mice and H-77/77 induced hypermotility in rats are behavioral signs related to the availability of noradrenaline at the receptor. 23 references. (Author abstract modified)

002206 Carney, John M.; Rosecrans, John A. Department of Pharmacology, College of Medicine, University of Oklahoma, Oklahoma City, OK 73190 **Effects of morphine and two enzyme resistant enkephalins on schedule-controlled responding in the rat.** Pharmacology Biochemistry and Behavior. 8(2):185-189, 1978.

To determine the effects of morphine and two enzyme resistant enkephalins on schedule controlled responding in the rat, water deprived rats were trained to respond for access to a water-filled dipper under a 20 response fixed-ratio schedule and were subsequently implanted with a lateral ventricle cannula and the effects of intraventricular injection of morphine, (N-methyl-tyrosyl)1 des COOH-Norleucyl5-Enkephalin, and (D-Ala)2 -- (des COOH-Norleucyl)5-Enkephalin were determined. All three compounds produced dose related decreases in FR20 responding. Morphine was about five times more potent than either of the two peptides while naloxone (1.0mg/kg, SC) antagonized the response rate decreasing effects of intraventricular morphine and two opiate peptides. Thus, the behavioral pharmacology of enkephalins is extended to include disruption of operant responding in the rat, which appears to an agonist effect of some narcotic receptor. 33 references. (Author abstract modified)

002207 Carruthers-Jones, D. I.; Depoortere, H.; Lowe, D. M. Biological and Medical Research Dept., Sandoz Ltd, CH-4202 Basel, Switzerland **Changes in the rat electrocorticogram following administration of two dihydrogenated ergot derivatives.** Gerontology (Basel). 24(Supplement 1):23-33, 1978.

In a paper presented at a workshop on experimental pharmacology of hydergine in Basel, December 1976, research on the comparative effects of dihydroergotoxine mesylate (DHET) and dihydro-beta-ergosine on the sleep/wakefulness cycle and the electrocorticogram power spectra of the rat is reported. DHET and dihydro-beta-ergosine altered the sleep/wakefulness cycle of the rat by increasing wakefulness and decreasing slow wave and rapid eye movement sleep. In addition, power spectrum analysis indicated that, in comparison with placebo, DHET increased total power. Dihydro-beta-ergosine increased relative power in the 4 to 8 Hz and in the 30 to 40 Hz bands of the electrocorticogram. The alterations in the sleep/wakefulness cycle and in the distribution of power in the rat electrocorticogram are discussed as possible indices of changes in alertness and attention. 25 references. (Author abstract modified)

002208 Carter, Carol Sue; Daily, Robert F.; Leaf, Russell. Department of Psychology, University of Illinois, Champaign,

IL 61820 **Effects of chlordiazepoxide, oxazepam, chlorpromazine, and d-amphetamine on sexual responses in male and female hamsters.** Psychopharmacology (Berlin). 55(2):195-201, 1977.

The acute effects on sexual behavior of oxazepam (16 to 64mg/kg), chlordiazepoxide (8 to 64mg/kg), chlorpromazine (2 to 8mg/kg), and d-amphetamine (0.8to 3.2mg/kg) were examined in intact male and femalle golden hamsters (Mesocricetus auratus). Intraperitoneal injections were given 45 min before the first behavioral test. In 10 min tests, lordosis was observed in estrous females both before and after copulation, and mounts, intromissions, and ejaculations were observed in males. Dose response related decrements in male sexual behavior were observed following chlorpromazine and chlordiazepoxide. All dose levels of oxazepam depress male sexual behavior. The highest dose of chlordiazepoxide and oxazepam attenuates the onset of female sexual behavior, and all dose levels reduce postcopulatory lordosis durations. Amphetamine does not interrupt either male or female sexual behavior, and chlorpromazine disrupts male but not female behavior. 33 references. (Author abstract)

002209 Chait, L. D.; Balster, Robert L. Department of Pharmacology, Box 726, MCV Station, Richmond, VA 23298 **The effects of acute and chronic phencyclidine on schedule-controlled behavior in the squirrel monkey.** Journal of Pharmacology and Experimental Therapeutics. 204(1):77-87, 1978.

To test the effects of phencyclidine (PCP), a study was conducted using five male squirrel monkeys trained to respond on a chain fixed-interval fixed-ratio schedule of food presentation. Acute PCP produced dose related decreases in response rate during both components of the schedule. Both components were equally affected by the drug. The effects of the drug on fixed-interval response rate were dependent on the control rate of responding in corresponding segments of the interval. After the initial dose/response determination, the subjects were placed on an individualized regimen of chronic PCP administration lasting from 82 to 126 days, beginning with daily injections for 2 days alternating with saline injections for 2 days, progressing to four injections daily. No evidence of physical dependence was seen upon withdrawal of the drug. Redetermination of the dose/response function for PCP demonstrated a nearly two, fold shift to the right of both the fixed-interval and fixed-ratio dose/response curves, indicating tolerance. In addition, the subjects' behavior recovered sooner from a dose of PCP given after the chronic regimen than from the same dose given before the chronic regimen. The results demonstrate that tolerance can occur to the behavioral effects of PCP in the squirrel monkey. 17 references. (Author abstract)

002210 Chance, William T.; Murfin, Diane; Krynock, Glenn M.; Rosecrans, John A. Dept. of Pharmacology, Medical College of Virginia, Virginia Commonwealth Univ., MCV Station, Box 726, Richmond, VA 23298 **A description of the nicotine stimulus and tests of its generalization to amphetamine.** Psychopharmacology (Berlin). 55(1):19-26, 1977.

The discriminative stimulus properties of nicotine were investigated under a variety of conditions in three separate experiments. In each experiment the subject's performance was assessed using a two lever operant procedure with liquid food reinforcement. In the first study rats were trained to discriminate between various doses of nicotine (100, 200, or 400 micrograms/kg) and saline under a VI-15s schedule of reinforcement. The second experiment investigated discrimination between 400 micrograms/kg of nicotine and saline under different schedules of reinforcement (VI-15s, FR-10, or DRL-10s). Generalization of the nicotine stimulus (400 micrograms/kg) to the stimulus effects of several doses of d-amphetamine (60, 120, 240, 480, and 720 micrograms/kg) was investigated in the third study. Dose generalization and time duration studies of the stimulus effects of nicotine indicate that the sensitivity of the rats to the nicotine cue was directly related to the training dose under the VI-15s schedule. Although response rates differed across the schedules of reinforcement, the rats' sensitivity to the stimulus effects of nicotine was not affected. Lack of complete generalization of the nicotine stimulus to d-amphetamine supports previous findings that these drugs were qualitatively different in relation to their discriminative control of behavior. 11 references. (Author abstract)

002211 Chance, William T.; Krynock, Glenn M.; Rosecrans, John A. Medical College of Virginia, Richmond, VA 23298 **Reduction of VMH lesion-induced hyperemotionality and antinociception by diazepam.** Federation Proceedings. 36(3):395, 1977.

Elicitation by ventromedial hypothalamic lesions of hyperemotionality and increased tail flick latencies to radiant heat in the rat was reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Septal lesions were previously observed to cause hyperemotionality and increased tail flick latencies in rats, but these behaviors returned to normal after several days' handling. Hyperemotionality and antinociception following ventromedial hypothalamic lesions were more resistant to the effects of daily handling than were these behaviors following septal lesions. Pretreatment with diazepam reduced both emotionality and tail flick latency 30 min later. The decreased response to heat in the lesioned rats seems to be secondary to hyperemotionality. 1 reference. (Journal abstract modified)

002212 Chippendale, Thomas John. Princeton University **Pharmacological influences on starvation-induced hyperresponsiveness in the rat. (Ph.D. dissertation).** Dissertation Abstracts International. Ann Arbor, MI, Univ. M-films, No. 77-21443 HC$15.00 MF$8.50 178 p.

Pharmacological influences on starvation-induced hyperresponsiveness in the rat were studied by investigating the behavioral, pharmacological, and biochemical nature of the presumptive change in amphetamine action that occurs after starvation, and possibly tracing antecedent physiological events. Seven experiments designed to characterize the changes in behavioral responsiveness that occur during fasting and to quantitatively analyze the starvation/amphetamine interaction failed to show that the neuropharmacological actions of amphetamine are altered by food deprivation and established that, in the fasted animal, specific forms of motor behavior are enhanced following changes in internal or external environment and that such changes are largely reactive in nature rather than spontaneously expressed. Further experiments showed that spiroperidol, a drug antagonistic to stimulants, was less potent in producing cataleptic behavior in food deprived rats, showing that drug effects are neither universally enhanced nor diminished by starvation. Further, serotonergic manipulations that might be expected to attenuate or modify starvation induced hyperresponsiveness fail to affect the phenomenon. Also, despite contrary circumstantial evidence, pituitary hormones appear to play no causative role in starvation hyperarousal. (Journal abstract modified)

002213 Clineschmidt, Bradley V.; Hanson, Harley M.; Pflueger, A. Barbara; McGuffin, Jodie C. Merck Institute for Therapeutic Research, West Point, PA 19486 **Anorexigenic and ancillary actions of MK-212 (6-chloro-2-(1-piperazinyl)-pyrazine; CPP).** Psychopharmacology (Berlin). 55(1):27-33, 1977.

The anorexigenic and ancillary actions of MK-212 (6-chloro-2-(1-piperazinyl)-pyrazine) were investigated in rats and cats. In rats allowed to eat for 2 hr/day and injected i.p. 30 min before feeding, MK-212, ED50 1.5mg/kg was two times more potent as an anorexigen than fenfluramine. However, the compounds were equiactive in the rat following p.o. administration 1.5or 3 hr before the test, while fenfluramine was more potent if the interval was extended to 6 hr. In cats permitted to eat for 3 hr/day, the ED50 dose (mg/kg p.o.)for MK-212 determined at 0.5, 1 and 3 hr after feeding was, respectively, 15, 10, and 3 times less than that of fenfluramine. Emesis and diarrhea were frequently observed ancillary effects in cats treated with fenfluramine, whereas apparent sedation and salivation were commonly detected in animals after MK-212. In rats or cats pretreated with methergoline, the decrease in food consumption elicited by MK-212 was markedly inhibited, suggesting that the mechanism of action involves a serotonin-like effect. Compared with the marked stimulant action of amphetamine, MK-212 had only a minor and inconsistent effect on motor activity in rats and mice. Similar results were obtained with fenfluramine. MK-212 was not self-administered by rats, while the self-administration of amphetamine and morphine were demonstrated using the same experimental protocol. 21 references. (Author abstract modified)

002214 Clineschmidt, Bradley V.; McGuffin, Jodie C. Merck Institute for Therapeutic Research, West Point, PA 19486 **Neurotensin administered intracisternally inhibits responsiveness of mice to noxious stimuli.** European Journal of Pharmacology (Amsterdam). 46(4):395-396, 1977.

The effect of intracisternal injections of neurotensin, a hypothalamic peptide, on responsiveness to noxious stimuli was examined in female mice. Results indicate that neurotensin administered intracisternally causes a dose related increase in stimulus response time upon exposure to the hot plate and a decrease in the frequency of writhing subsequent to the injection of acetic acid. The antinocisponsive action of neurotensin lasted for about 1 hour following the maximum effective dose (250ng/mouse) and for approximately 2 hours when this dose was increased tenfold. Naloxone (1mg/kg) was not effective as an antagonist of the antinocisponsive action of neurotensin 2.5ng/mouse (hot plate) or 2.5ng/mouse (writhing). The reduction of body temperature by oxotremorine (0.1mg/kg), chlorpromazine (4mg/kg), or D,L-5-hydroxytryptophan (300mg/kg) had no effect on the reaction time. 5 references.

002215 Cohn, Major L.; Cohn, Marthe; Taylor, Floyd H. Univ. of Pittsburgh, Magee-Womens Hospital, Forbes Avenue and Halket St., Pittsburgh, PA 15213 **Guanosine 3',5'-monophosphate: a central nervous system regulator of analgesia.** Science. 199(4326):319-322, 1978.

A research project on guanosine 3',5-monophosphate as a central nervous system regulator of analgesia is reported. In experiments with rats it was found that the dibutryl derivative of guanosine 3',5'-monophosphate (cyclic-GMP), administered centrally, totally abolishes response to noxious stimuli without depressing the central nervous system, and analgesic properties of the nucleotide are not reversed by naloxone. Microinjected intracerebrally into different sites, dibuyryl cyclic-GMP does not mimic the action of morphine. Pharmacological effects of dibutyryl cyclic-GMP suggest that endogneous cyclic-GMP modulates an inhibitory pain pathway distinct from that on which morphine acts. 28 references. (Author abstract)

002216 Collins, Robert L.; Whitney, Glayde. Department of Psychology, Florida State University, Tallahassee, FL 32306 **Genotype and test experience determine responsiveness to morphine.** Psychopharmacology (Berlin). 56(1):57-60, 1978.

To examine the extent to which observed differences in responsiveness to morphine across genotypes and across test situations are affected by differences in susceptibility to experience effects, initial responsiveness to morphine was studied in two inbred strains of mice, C57BL/6J and DBA/2J, and their F1 hybrid, using both a hot plate analgesia test and a locomotor activity test. Three dose levels of morphine were used, 0mg/kg, 5mg/kg, and 15mg/kg. The inclusion of the 0mg/kg group revealed differences between the inbred strains in the effects of test experience. These data also led to some new conclusions about the differences in responsiveness to morphine between the strains studied. On both tests, the DBA mice showed no effect of morphine, the C57 mice showed large effects, and the F1 mice showed an intermediate effect. 12 references. (Author abstract modified)

002217 Colpaert, Francis C.; Niemegeers, Carlos J. E.; Janssen, Paul A. J.; Van Ree, Jan M. Dept. of Pharmacology, Janssen Pharmaceutica, Beerse, Belgium **Narcotic cueing properties of intraventricularly administered sufentanil, fentanyl, morphine and met-enkephalin.** European Journal of Pharmacology (Amsterdam). 47(1):115-119, 1978.

The narcotic cueing activity of sulentanil, ventanyl, morphine, and met-enkephalin was studied upon their injection into the lateral brain ventricle of the rat trained to discriminate fentanyl from saline. Comparative studies on the analgesic activity of these narcotics support the hypothesis that there exists a close correlation between the narcotic cueing and the analgesic activity of narcotic drugs. 8 references. (Author abstract modified)

002218 Cooper, Barrett R.; Konkol, Richard J.; Breese, George R. Department of Pharmacology, Burroughs-Wellcome Company, Research Triangle Park, NC 27709 **Effects of catecholamine depleting drugs and d-amphetamine on self-stimulation of the substantia nigra and locus coeruleus.** Journal of Pharmacology and Experimental Therapeutics. 204(3):592-605, 1978.

6-Hydroxydopamine treatments which preferentially depleted either norepinephrine (NE) or dopamine (DA) were used to define the importance of these transmitter systems in the behavioral alterations produced by catecholamine synthesis inhibitors and d-amphetamine on self-stimulation of the locus coeruleus (LC) and substantia nigra (SN). After chronic reduction of brain DA, an acute depression of self-stimulation of both the LC and SN occurred. Preferential depletion of NE with 6-hydroxydopamine did not result in a significant decrease in self-stimulation of LC or SN. Alpha-methyltyrosine caused a significant reduction in responding at both electrode placements in animals depleted of brain DA. Administration of U-14,624 affected neither SN nor LC self-stimulation, even though it produced an additional 70% depletion of NE. When d-amphetamine sulfate was given to 6-hydroxydopamine treated rats, the facilitation of self-stimulation produced by this compound was significantly attenuated in rats with prior depletion of brain DA. d-Amphetamine actions in animals pretreated with reserpine were found to be antagonized by alpha-methyltyrosine but not by U-14,624. Results suggest that drugs can alter self-stimulation of a site in

brain anatomically associated with noradrenergic neural pathways and self-stimulation of a site primarily associated with dopaminergic pathways in a similar manner. These data also provided evidence for the involvement of DA fibers in the pharmacological actions of d-amphetamine, reserpine and alpha-methyltyrosine. 56 references. (Author abstract modified)

002219 Corum, C. Ronald; Thurmond, John B. Inst. of Physical Medicine and Rehabilitation, Louisville, KY 40202 **Effects of PCPA and selective REM sleep deprivation on rotorod performance and open-field behavior in the rat.** Bulletin of the Psychonomic Society. 11(4):251-254, 1978.

The effects of p-chlorophenylalinine (PCPA) administration or of selective REM sleep deprivation (REMD) on open-field behavior and rotorod performance in rats were examined. Baseline performance and behavior were obtained over 10 days, then treatments were administered for 12 days, and recovery was measured over 5 days. Both PCPA and REMD produced shorter emergence latencies in the open-field and increased locomotor activity and rearing. The effects of PCPA occurred during the first 6 days after injection, whereas the effects of REMD occurred during the last 6 days of the 12 day treatment period. Data suggest that although PCPA and REMD produced similar changes in behavior, different mechanisms may have been involved. (Author abstract)

002220 Costall, Brenda; Naylor, Robert J.; Owen, Richard T. Postgraduate School of Studies in Pharmacology, University of Bradford, Bradford BD7 1DP, West Yorkshire, England **Behavioural correlates of modified dopaminergic/anticholinergic responses following chronic treatment with neuroleptic agents of differing activity spectra.** European Journal of Pharmacology (Amsterdam). 48(1):29-36, 1978.

An attempt was made to differentiate the mechanisms of action of those neuroleptic agents having antidyskinetic properties from the classical neuroleptics by studying the effects of chronic treatment on the responses to a dopamine agonist and cholinergic antagonist. Rats were chronically treated with haloperidol (2mg/kg i.p.), oxiperomide (8mg/kg i.p.), pimozide (8mg/kg p.o.), tiapride (100mg/kg i.p.), sultopride (100mg/kg i.p.), sulpiride (100mg/kg p.o.)and metoclopramide (100mg/kg i.p.)for 7 consecutive days. On days 1, 3 and 7 after neuroleptic withdrawal rats were assessed for their sensitivity to the stereotypic effects of apomorphine (0.25 to 1.0mg/kg s.c.)and the locomotor stimulant effects of dexetimide (0.32 to 1.25mg/kg s.c.). A supersensitivity phase to apomorphine, persisting for 1 to 3 days, was noted in all drug treated groups and, during this time, the responses to dexetimide were decreased (haloperidol, oxiperomide and pimozide groups), increased (metoclopramide group) or remained similar to control values (sultopride, sulpiride, and tiapride treated animals). The responses to dexetimide returned to control values in all treatment groups as the apomorphine sensitivity phase declined. It is suggested that chronic treatment with neuroleptic agents may enhance the sensitivity of those cerebral receptors responsible for mediating the stereotypic effects of apomorphine, and that the relationship between such dopamine function and interacting cholinergic mechanisms may differ for the different groups of neuroleptic agent. 19 references. (Author abstract)

002221 Costentin, Jean; Marcais, Helene; Protais, Philippe; Schwartz, Jean-Charles. Laboratoire de Pharmacodynamie et Physiologie, U.E.R. de Medecine et de Pharmacie, 49, rue Maulevrier, F-76000 Rouen, France **Tolerance to hypokinesia elicited by dopamine agonists in mice: hyposensitization of autoreceptors?** Life Sciences (Oxford). 20(5):883-886, 1977.

Development of hypokinesis or hyperkinesis in male Swiss albino mice pretreated with apomorphine was studied. Locomotor activity was measured on treadmills or in activity cages equipped with photoelectric cells. In saline pretreated mice weighing a low dose of apomorphine caused hypokinesia; this effect tended to disappear with apomorphine in dosage double the first. Mice pretreated with a high apomorphine dose did not show hypokinesia to the low dose. Piribedil, a weak dopamine agonist, caused a decrease in motor activity in saline pretreated mice, but not in apomorphine pretreated animals. In control animals, low doses of amphetamine decreased motor activity, but higher doses caused hyperkinesia. In apomorphine pretreated mice, the amphetamine induced hyperkinesia was suppressed, but the hyperkinesia was still present. Results may be explained by the assumption that following autoreceptor stimulation, hyposensitivity develops on autoreceptors regulating the activity of dopaminergic neurons, whereas the sensitivity of postsynaptic receptors is not modified. 18 references.

002222 Crowley, William R.; Nock, Bruce L.; Feder, Harvey H. Institute of Animal Behavior, Rutgers University, 101 Warren St., Newark, NJ 07102 **Facilitation of lordosis behavior by clonidine in female guinea pigs.** Pharmacology Biochemistry and Behavior. 8(2):207-209, 1978.

Studies were conducted to determine the effects of clonidine on lordosis behavior in female guinea-pigs, specifically, whether clonidine induced a refractory period comparable to that effected by progesterone, and whether clonidine enhances lordosis responding when given during the decline in receptivity or during the refractory period. Lordosis behavior was induced in previously unreceptive, ovariectomized estrogen-primed female guinea-pigs by administration of the noradrenergic agonist clonidine. Clonidine also enhanced lordosis responding in females that were weakly receptive after estrogen priming. Unlike progesterone, the lordosis facilitating effect of clonidine was not accompanied by a subsequent refractory period. Clonidine had a weak lordosis facilitatory effect when administered during the decline in receptivity to estrogen plus progesterone-primed animals and failed to induce lordosis when administered during the refractory period. Differences between the lordosis effects of clonidine and progesterone are elucidated. 12 references. (Author abstract modified)

002223 Davis, Kenneth L.; Hollister, Leo E.; Tepper, Jonathan. Veterans Administration Hospital, Palo Alto, CA 94304 **Cholinergic inhibition of methylphenidate-induced stereotypy: oxotremorine.** Psychopharmacology (Berlin). 56(1):1-4, 1978.

To examine the efficacy of the central muscarinic agonist, oxotremorine, as a method for increasing cholinergic activity, and to establish toxicity of dosage levels, female mice were given oxotremorine in dosages between 0.1and 20mg/kg and inhibition of methylphenidate induced stereotypy by oxotremorine (0.05, 0.1, and 0.5mg/kg) was assessed in a second group of mice. Doses of 0.05 to 0.5were found to inhibit stereotypy and produced such minimal side-effects that a peripheral anticholinergic was unnecessary. The lethal dose was found to be 12.5mg/kg with death occurring 20 to 25 minutes postinjection. Lethality required 250 times the dose that was effective for inhibiting methylphenidate induced stereotypy. A number of lines of evidence indicate that increasing central cholinergic activity may be useful in various

psychiatric syndromes and movement disorders. A relatively safe oral cholinomimetic would be clinically useful. Oxotremorine may be such an agent. 22 references. (Author abstract modified)

002224 De Wit, Harriet; Wise, Roy A. no address **Blockade of cocaine reinforcement in rats with the doapmine receptor blocker pimozide, but not with the noradrenergic blockers phentolamine or phenoxybenzamine.** Canadian Journal of Psychology (Toronto). 31(4):195-203, 1977.

Rats self-administering cocaine were treated with the dopamine receptor pimozide or the noradrenergic blockers phentolamine or phenoxybenzamine. Pimozide caused a dose related (.0625 to .5mg/kg) acceleration of responding; at the higher doses responding consequently dropped out. These effects of pimozide parallel the known effects of reward (unit dose) reduction and reward termination and thus suggest an important role for dopaminergic brain mechanisms in the mediation of cocaine reinforcement. Neither phenoxybenzamine given systematically nor phentolamine given intraventricularly had similar effects; thus no similar role for noradrenergic brain mechanism was suggested by these experiments. 25 references. (Author abstract)

002225 Edmonds, Don E.; Gallistel, C. R. no address **Reward versus performance in self-stimulation: electrode-specific effects of alpha-methyl-p-tyrosine on reward in the rat.** Journal of Comparative and Physiological Psychology. 91(5):962-974, 1977.

Reduction of brain stimulation reward by alpha-methyl-p-tyrosine (AMPT) was tested, using a measure of reward previously shown to be relatively unaffected by variables that alter performance but not reward. The rewarding effectiveness of stimulation was determined by the location of the sharp rise in the function relating running speed in an alley to the nember of pulses received as a reward. For some electrodes, AMPT depressed self-stimulation performance (speed of running) without producing any sizable effect on the measure of reward (location of rise). For other electrodes, the rewarding effectiveness of the stimulation was greatly reduced by AMPT and restored by L-DOPA. These opposing results could be repeatedly demonstrated on different electrodes in the same rat. The electrode specific differential sensitivity to AMPT suggests neurochemically disparate substrates for reward. 17 references. (Author abstract modified)

002226 El-Yousef, M. K.; Steranka, L.; Sanders-Bush, E. Pinellas Horizon Mental Health Center and Hospital, P.O. Box 5989, Clearwater, FL 33518 **Rapid tolerance to the motor effects of p-chloroamphetamine in rats.** Psychopharmacology (Berlin). 55(2):109-114, 1977.

A series of studies was undertaken to determine if tolerance to the effect of p-chloroamphetamine (PCA) on motor activity in rats would develop with repeated injections, and the effects of single or repeated doses of PCA on the in vitro synaptosomal uptake of labeled norepinephrine(3H-NE) and labeled dopamine (3H-DA) and the in vivo metabolism of intraventricularly administered 3H-NE and 3H-DA. The administration of 10mg/kg of PCA induces a complex behavioral syndrome, which was quantified by scoring specific symptoms after direct observation. In agreement with previous data, this syndrome appears to be mediated by a release of 5-hydroxytryptamine (5-HT) since pretreatment with PCA prevented its development on subsequent injection of the drug. After the administration of lower doses of PCA, total motor activity as measured in activity cages increases, and tolerance to this effect also develops rapidly. Moreover, the degree of tolerance is the same if the time between the 2 injections is 1 day or 2 weeks, suggesting that 5-HT release is also involved in the tolerance to the motor effects of lower doses of the drug. Moreover, biochemical studies of the response of catecholaminergic neurons to PCA suggest that tolerance does not develop to the effects on DA and NE neurons on repeated injection of PCA. 32 references. (Author abstract modified)

002227 Elchisak, Mary A.; Rosecrans, John A. Dept. of Pharmacology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23220 **Effects of 6-hydroxydopamine-induced depletions of brain catecholamines or dopamine on meperidine antinociception in rats.** Pharmacology (Basel). 16(3):142-147, 1978.

The participation of brain norepinephrine (NE) and dopamine (DA) in the production of the antinociceptive effect of meperidine was investigated. Rats were permanently depleted of brain catecholamines via 6-hydroxydopamine treatments at 2 weeks of age. The antinociceptive activity of meperidine was determined 6 to 8 weeks later in control, NE depleted and DA depleted, and DA depleted rats by both the tail flick and hot plate methods. The antinociceptive activity of meperidine was reduced in DA depleted male rats. In DA depleted female rats, however, the antinociceptive activity was increased at low doses of meperidine and decreased only at higher doses of the drug. In male NE + DA depleted rats, the activity was generally intermediate between that seen in DA depleted and control rats. No consistent change in the activity of meperidine was observed in female NE + DA depleted rats. 16 references. (Author abstract modified)

002228 Everitt, B. J. Dept. of Anatomy, Univ. of Cambridge, Cambridge, England **Effects of clomipramine and other inhibitors of monoamine uptake on the sexual behaviour of female rats and rhesus monkeys.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):202-210, 1977.

Studies of sexual activity and of 5-hydroxytryptamine (5-HT) and noradrenalin (NA) uptake were performed in female rats and monkeys exposed to clomipramine, protriptyline and other agents to provide insight into their effects on human sexual activity. In female rhesus monkeys, clomipramine decreased sexual receptivity to very low levels, closely related to the period of drug administration and to inhibition of 5-HT and NA uptake. These findings are not conclusive, but it is strongly suggested that a subhuman primate behavioral model may prove to be a very important one for an understanding of the sexual side-effects of psychoactive drugs in man. An urgent need for more precise clinical evaluation of sexual behavior disorders is expressed. 24 references. (Author abstract modified)

002229 Ezrin-Waters, Cheryl; Seeman, Philip. Dept. of Pharmacology, University of Toronto, Toronto, Ontario M5S 1A8, Canada **L-dopa reversal of hyperdopaminergic behaviour.** Life Sciences (Oxford). 22(12):1027-1031, 1978.

To determine whether tardive dyskinesia may stem from a neuroleptic induced dopaminergic supersensitivity, male Wistar rats were pretreated with reserpine to produce supersensitive responses of apomorphine induced sniffing, and were then treated with L-dopa and carbidopa for 4 days. L-dopa/carbidopa treatment reversed the apomorphine supersensitivity. This reversal suggests that the treatment may be of some benefit in tardive dyskinesia. 57 references. (Author abstract modified)

002230 Ferko, A. P.; Pack, R. L. Hahnemann Medical College, Philadelphia, PA 19102 **The effect of ethanol on suppression of the naloxone precipitated escape response in morphine dependent mice.** Federation Proceedings. 36(3):286, 1977.

The effects of ethanol, pyrazole, ethanol plus pyrazole, and pentobarbital on the naloxone precipitated escape response were studied in morphine dependent mice, and results will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Morphine dependence was produced in mice by administration of 399mg/kg morphine over a 2 day period. Ethanol, 2 to 3g/kg, which produced a mean blood concentration of 1.88 to 3.28mg/ml, suppressed the escape response. When pyrazole was given to morphine dependent mice, ethanol reduced or abolished the naloxone precipitated escape response. Pentobarbital given to morphine dependent mice prevented the jumping behavior following naloxone injection. Thus, ethanol is not unique in suppressing the escape response. (Journal abstract modified)

002231 Ferri, S.; Reina, R. Arrigo; Spadaro, C.; Braga, P. Institute of Pharmacology, Faculty of Pharmacy, University of Catania, Catania, Italy **6-hydroxydopamine inhibits some effects of mescaline centrally administered to rabbits.** Psychopharmacology (Berlin). 55(2):147-149, 1977.

To examine the effects of 6-hydroxydopamine (6-OHDA) pretreatment on behavioral effects of mescaline and to elucidate the role of catecholamines in these effects, stereotypy and licking behavior in rabbits was assessed following central administration of 100 microgram/kg mescaline with or without 6-OHDA pretreatment. The narcotic antagonist naloxone does not antagonize antinociception whereas pretreatment with 6-OHDA inhibits this mescaline effect. Stereotyped behavior of rabbits following central mescaline administration is also prevented by 6-OHDA pretreatment. Since 6-OHDA is known to produce a degeneration of catecholamine containing nerve terminals, a crucial role of catecholamines is suggested in the complex of effects seen in the rabbit after central administration of the hallucinogen. 12 references. (Author abstract modified)

002232 Flood, James F.; Bennett, Edward L.; Orme, Ann E.; Rosenzweig, Mark R.; Jarvik, Murray E. Dept. of Psychiatry, UCLA, Los Angeles, CA 90024 **Memory: modification of anisomycin-induced amnesia by stimulants and depressants.** Science. 199(4326):324-326, 1978.

To determine whether excitant drugs could counteract the amnesic effects caused by inhibition of cerebral protein systhesis and whether depressant drugs could enhance amnesia, a study was conducted. When administered after training, in a passive (footshock) avoidance task, the stimulants caffeine or nicotine blocked amnesia for the task that had been produced by injections of the protein synthesis inhibitor anisomycin given prior to training. With footshock at a higher intensity, anisomycin did not produce amnesia by itself, but the administration of the depressants chloral hydrate or sodium phenobarbital after training did not have an appreciable influence on the overall degree of protein synthesis inhibition produced by anisomycin. The results support the hypothesis that arousal is an important factor in the conversion of short-term to long-term memory. 6 references. (Author abstract modified)

002233 Flood, James F.; Vidal, Daniel; Bennett, Edward L.; Orme, Ann E.; Vasquez, Sergio; Jarvik, Murray E. Dept. of Psychiatry, UCLA, Los Angeles, CA 90024 **Memory facilitating and anti-amnesic effects of corticosteroids.** Pharmacology Biochemistry and Behavior. 8(1):81-87, 1978.

The effects of corticosterone, hydrocortisone and dexamethasone on retention of active and passive avoidance training were studied in male mice. Posttraining administration of any of the hormones facilitated subsequent retention test performance of poorly trained mice when tested 1 week after training and drug administration. The optimum dose of dexamethasone was 4mg/kg, while corticosterone and hydrocortisone were effective at 30 and 40mg/kg, respectively. Dexamethasone significantly facilitated retention when administered up to 150 min but not at 210 min after training. It was further determined that dexamethasone blocked the amnesic effect of two but not four successive injections of anisomycin in both active and passive avoidance tasks. Corticosterone and dexamethasone when administered to anisomycin injected mice caused only a small, transient increase in the protein synthesis inhibition. In saline-injected control mice, the hormones also caused a small inhibition of protein synthesis which disappeared quickly. Plasma corticosterone levels were measured in mice trained and given anisomycin, cycloheximide or saline. Plasma corticosterone levels were reduced 43% by anisomycin and 80% by cycloheximide. In both cases the corticosterone levels subsequently increased rapidly after the inhibitor injection and were elevated by about five times above control levels at 130 min after the inhibitor injection. The results are discussed in terms of the effect of central stimulant action of corticosteroids on memory formation. 33 references. (Author abstract)

002234 Fowler, Stephen C.; Price, A. W. Dept. of Psychology, University of Mississippi, University, MS 38677 **Some effects of chlordiazepoxide and d-amphetamine on response force during punished responding in rats.** Psychopharmacology (Berlin). 56(2):211-215, 1978.

To determine the effects of chlordiazepoxide and d-amphetamine on response force during punished responding, rats were reinforced with water on a continuous reinforcement schedule and were also punished with electric shock for every fifth response applied to a silent, isometric, force sensing manipulandum. Oral doses of chlordiazepoxide (3.0, 9.0, 27.0mg/kg) increased both conventional rate and force of punished responding. In contrast, d-amphetamine (0.8, 1.6, 3.2mg/kg, by gavage) further decreased conventional rate and force of response, but this latter drug increased the rate of recorded responses that were lower than the 15g force criterion for response consequences. The results for chlordiazepoxide are viewed in terms of its anxiolytic properties, while the d-amphetamine data appear to support a theory of amphetamine effects based on the concept of stereotyped behaviors. 17 references. (Author abstract modified)

002235 Gerald, Michael C.; Gupta, Tribhuwan K. Div. of Pharmacology, College of Pharmacy, Ohio State Univ., 500 W. 12th Ave., Columbus, OH 43210 **The effects of amphetamine isomers on rotarod performance.** Psychopharmacology (Berlin). 55(1):83-86, 1977.

The effect of amphetamine isomers on the rotarod performance of rats was studied, and the influence of neostigmine on the amphetamine induced behavior was assessed. Amphetamine isomers impaired the rotarod performance of rats in a dose related manner, with (+)-amphetamine approximately four times as potent as its (-)-isomer. Coadministration of the peripheral cholinesterase inhibitor neostigmine salicylate (0.005mg/kg) attenuated (+)-amphetamine neurotoxicity. Results, in conjunction with previously reported effects of the

drug on isolated nerve muscle preparations, suggest that the muscle weakness produced by high doses of amphetamine may result from inhibition of transmission at the neuromuscular junction. 17 references. (Author abstract modified)

002236 Gessner, Peter K.; Dankova, Jana B. Department of Pharmacology, State University of New York at Buffalo, Buffalo, NY 14214 **The role of serotonin antagonism in the tremorgenic action of bufotenine in mice.** Federation Proceedings. 36(3):352, 1977.

The role of serotonin in the tremorgenic effect of bufotenine in mice will be discussed at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Acetyl bufotenine was administered to mice injected 72, 48, and 24 hr prior with p-chlorophenylalanine, and tremorgenic activity was determined ballistographically 30 to 120 sec after acetyl bufotenine administration. Pretreatment with p-chlorophenylalanine significantly enhanced the observed tremor, while pretreatment 1 hr prior with l-5-hydroxytryptophan attenuated the bufotenine tremor. Thus the tremorgenic effect of bufotenine is mediated by antagonism of serotonin. Dopa blocked the tremorgenic effects of LSD and 5-methoxy-N,N-dimethyltryptamine. Administration of dopa 7.5to 60 min prior also blocked bufotenine tremor. The dopa induced decline in brain serotonin followed the time course of the dopa induced attenuation of bufotenine tremor, suggesting that attenuation of the tremor could be mediated by displacement of serotonin by dopamine formed from dopa. 1 reference. (Journal abstract modified)

002237 Gray, Gary D. Dept. of Physiology, Stanford Univ., Stanford, CA 94305 **Differential effects of the antiandrogen flutamide on aspects of sexual behavior in castrated, androgen-treated male rats.** Psychoneuroendocrinology (Oxford). 2(4):315-320, 1977.

The question of whether the behavioral effects of the nonsteroidal antiandrogen flutamide result from actions on CNS or peripheral mechanisms governing sexual behavior in male rats is researched. Restoration of sexual behavior in long-term male castrates was evaluated in response to administration of testosterone propionate (TP) with or without flutamide. Two types of behavioral tests were employed -- a standard test of the complete copulatory behavior pattern and anesthetization of the male's penis which served to reduce the role of peripheral factors in the male's behavior and eliminate intromission and ejaculatory behavior. In the behavioral tests with genital anesthetization, flutamide facilitated mounting behavior. Since mounting behavior in these tests presumably represents CNS function, facilitation of the behavior indicates that flutamide acts as an androgen, and not as an antiandrogen, on CNS mechanisms. In the behavioral tests of the complete copulatory behavior pattern, flutamide inhibited ejaculation and, to a lesser extent, intromission behavior. Flutamide also completely inhibited the stimulatory effect of TP on peripheral structures. It was concluded that the inhibitory effect of flutamide on ejaculation behavior resulted from deficiencies or peripheral, especially penile, structures although an alternative possibility -- that flutamide differentially affects two CNS mechanisms governing mounting and ejaculation -- cannot be excluded. 8 references. (Author abstract)

002238 Guzek, Jan W. Zaklad Patofizjologii, Akademia Medyczna, 90-136 Lodz, Narutowicza 60, Poland **Monoaminergic influences on the incorporation of 35S in the hypothalamic and neurohypophysial proteins following intracerebroventricular injection of 35S-cysteine in dehydrated rats.** Acta Physiologica Polonica (Warszawa). 28(2):93-99, 1977.

A study of the monoaminergic influences on the incorporation of 35S in the hypothalamic and neurohypophysial proteins following intracerebroventricular injection of 35S-cysteine in dehydrated rats is presented. In the rats dehydrated for 48 hr the mean specific activity of hypothalamic and neurohypophysial TCA precipitable proteins following intracerebroventricular injection of L-cysteine-35S-hydrochloride was significantly higher than that found in the dehydrated and reserpinized. Under influence of amphetamine sulfate, however, no change of 35S uptake by TCA precipitable hypothalamic and neurohypophysial proteins could be detected in rats similarly dehydrated. 34 references. (Journal abstract modified)

002239 Hammerbeck, D. M.; Mitchell, C. L. Riker Laboratories Inc., 3M Company, 3M Center, St. Paul, MN 55101 **The reinforcing properties of procaine and d-amphetamine compared in rhesus monkeys.** Journal of Pharmacology and Experimental Therapeutics. 204(3):558-569, 1978.

To compare reinforcing properties of procaine and d-amphetamine, 12 rhesus monkeys were studied under a fixed-ratio (FR) schedule of intravenous procaine or d-amphetamine injection for 8 hrs. daily. Under the FR schedule, every nth lever press produced an injection. The FR value (n) and the dose per injection of procaine and d-amphetamine were varied systematically. At a FR value of 10, responding was maintained by doses of procaine ranging from 0.125 to 12mg/kg/injection and by doses of d-amphetamine ranging from 0.01 to 0.1mg/kg/injection. At doses of 1mg/kg/injection of procaine and 0.1mg/kg/injection of d-amphetamine, responding was maintained at FR value up to 100 by procaine and d-amphetamine but not by saline. Responding and drug intake were relatively constant throughout each 8 hour session with procaine, but responding tended to decrease and was more variable over the session with d-amphetamine. No toxic effects were observed in doses up to 6mg/kg/injection with procaine. At this dose, eating and drinking ceased during the period of access to the drug. One of the four monkeys died at 8mg/kg/injection of procaine. At 12mg/kg/injection all three monkeys tested showed signs of toxicity. 18 references. (Author abstract modified)

002240 Hansult, Carole; Balopole, Donna; Scouten, Charles. no address **Effects of prolactin, dexamethasone, and corticosterone on maternal aggression and infant care.** Behavior Genetics. 8(1):97, 197?.

The possible permissive role of corticosterone in maternal aggression and care is studied in mice on the basis of previous studies of the role of prolactin in promoting maternal aggression. It is noted that because of the location of the laboratory, BALBc/bJ mice were substituted for the usually used BALBc/bCRGL mice, and these mice showed lower attack frequencies. Subjects were tested for aggression against a male intruder. C57's which attacked and BALB's which did not were discarded. Mothers were tested the day they gave birth and given either prolactin, prolactin/corticosteroid, corticosteroid, dexamethasone, or saline once a day for 7 days and then tested for aggression. During this time maternal care was observed. BALBc/bJ mice showed no effect of any treatment. C57's showed a depression in maternal care under dexamethasone and an increase in aggression under both prolactin and prolactin/corticosterone. BALBc/bCRGL mice showed a decrease in maternal care under dexamethasone but no other effects. It appears that BALBc/bCRGL and BALBc/bJ mice have developed significant differences in maternal aggression over the years and in maternal care. (Journal abstract modified)

002241 Harrigan, Stephen E.; Downs, David A. Warner-Lambert Pharmaceutical Research Div., Dept. of Pharmacology, 2800 Plymouth Road, Ann Arbor, MI 48105 **Continuous intravenous naltrexone effects on morphine self-administration in rhesus monkeys.** Journal of Pharmacology and Experimental Therapeutics. 204(2):481-486, 1978.

Continuous intravenous naltrexone effects on morphine self-administration were studied in the rhesus monkey. Results indicate that continuous naltrexone infusions can produce stable, long-term suppression of previously high rates of morphine self-administration in monkeys. Further, infusion rates above 5 micrograms/kg/hr of naltrexone blocked morphine self-administration over a wide range of doses. The degree of suppression morphine self-administration at 8 micrograms/kg/injection was directly related to the rate of naltrexone infusion. These results support the hypothesis that chronic antagonist treatment at sufficient levels can block narcotic reinforcing effects and attenuate opiate seeking behavior. 16 references.

002242 Harris, R. Adron. Department of Pharmacology, University of Missouri Medical Center, Columbia, MO 65201 **Effects of ethanol: alteration by inorganic ions and naloxone.** Federation Proceedings. 36(3):285, 1977.

Paper presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977, reported effects of calcium ion and naloxone in ethanol effects in mice and rats. Administration of calcium gluconate or calcium chloride to mice 20 min before i.p. injection of 4g/kg ethanol doubled sleeping times. Calcium ion decreased ethanol ED-50 for loss of righting reflex. Ethanol sleeping times were increased by manganese, but were not affected by magnesium ion, magnesium gluconate, lanthanum ion, or verapamil. Ethanol induced hypothermia was reduced by lanthanum ion and increased by manganese ion, but was not altered by calcium ion, magnesium ion, or verapamil. Naloxone did not alter the hypothermic effects of ethanol, the ED-50 of ethanol for loss of righting reflex, or the duration of loss of righting reflex in mice. In rats naloxone s.c. potentiated the decreasing rate induced by ethanol on responding under a 2 min fixed-interval schedule of food reinforcement. 1 reference. (Journal abstract modified)

002243 Harris, R. Adron; Snell, Diane; Loh, Horace H. Department of Pharmacology, University of Missouri Medical Center, Columbia, MO 65201 **Effects of stimulants, anorectics, and related drugs on schedule-controlled behavior.** Psychopharmacology (Berlin). 56(1):49-55, 1978.

The effects of nine drugs (stimulants, anorectics, and related drugs) were studied in rats responding under either fixed-ratio 30 (FR30) or fixed-interval 2 min (FI2) schedules of food presentation. All the drugs decreased average rates of responding under both schedules in a dose related manner, with apomorphine and clonidine being the most potent and caffeine the least potent. d-Amphetamine was about three times more potent than l-amphetamine in decreasing responding under the FR schedule, while the two isomers were equipotent in reducing the average response rates under the FI schedule. A 10mg/kg dose of fenfluramine decreased responding for 2 or 3 days after administration, but this treatment did not produce long lasting changes in control performance or in the effects of the serotonergic drugs quizapine and d-p-methoxyamphetamine. The effects of the drugs on the local rates of responding during the FI may be divided into three categories: .) those drugs that increased low rates of responding and decreased high rates of responding (rate dependent effects) at dosages that did not markedly decrease the average response rates (d-amphetamine, methylphenidate, and cocaine); 2) those that produced rate dependent effects only at dosages that markedly reduced average response rates (fenfluramine, quipazine, and clonidine); and 3) those that did not produce clear rate dependent effects at any dose tested (l-amphetamine, apomorphine, and caffeine). These behavioral results are discussed in relation to their known biochemical effects on brain catecholamine and serotonin systems. 38 references. (Author abstract)

002244 Harris, R. Adron; Snell, Diane; Loh, Horace H. Dept. of Pharmacology, Univ. of Missouri, M523 Medical Sciences Bldg., Columbia, MO 65201 **Effects of d-amphetamine, monomethoxyamphetamines and hallucinogens on schedule-controlled behavior.** Journal of Pharmacology and Experimental Therapeutics. 204(1):103-117, 1978.

To test the effects of 16 drugs, including d-amphetamine, monomethoxyamphetamines and various hallucinogens, on schedule controlled behavior of rats responding under fixed-ratio (FR30) and fixed-interval (FI 2 min) schedules of food presentation, a study was conducted. The drugs tested included lysergic acid diethylamide (LSD), dimethyltryptamine, mescaline, d-amphetamine and 12 methoxylated amphetamines. All of the drugs decreased the average rates of responding under both schedules; but their potencies varied widely. For the 12 drugs which are known to produce hallucinogenic effects, their potencies in reducing responding were positively correlated with their reported potencies in producing these subjective effects in humans. Analysis of responding under the FI schedule indicated that d-amphetamine, m-methoxyamphetamine, p-methoxyamphetamine, LSD and 3,4-methylenedioxyamphetamine generally increased the low rates of responding occurring at the beginning of each interval and decreased the high rates of responding occurring later in each interval (rate dependent effects). The other drugs generally decreased responding throughout the interval. It was concluded that the data suggest that rate dependent effects may be produced by activation of catecholamine systems and inhibited by stimulation of serotonergic systems. 52 references. (Author abstract modified)

002245 Havlicek, V.; Rezek, M.; Leybin, L.; Friesen, H. Department of Physiology, University of Manitoba, Winnipeg, Manitoba R3E OW3, Canada **Analgesic effect of cerebroventricular administration of somatostatin (SRIF).** Federation Proceedings. 36(3):363, 1977.

Possible analgesic properties of somatostatin in male Sprague-Dawley rats will be discussed at the 61st annual meeting of the Federation of American Societies of Experimental Biology, Chicago, 1977. Somatostatin, 1 or 10 micrograms, was injected intraventricularly and analgesia was measured by hot immersion tail flick. Both doses significantly prolonged the tail flick response, prolongation being 21% with low dose and 38% at high dose. The D-tryptophan analogue of somatostatin caused a 16% prolongation at a dose of 10 micrograms. Somatostatin may act by partially binding to opiate receptors. 1 refernce. (Journal abstract modified)

002246 Headley, P. M.; Duggan, A. W.; Griersmith, B. T. Department of Pharmacology, John Curtin School of Medical Research, Australian National University, Canberra City, ACT 2601, Australia **Selective reduction by noradrenaline and 5-hydroxytryptamine of nociceptive responses of cat dorsal horn neurones.** Brain Research (Amsterdam). 145(1):185-189, 1978.

A series of experiments was undertaken to elucidate the effects of noradrenaline (NA) and 5-hydroxytryptamine (5-HT), ejected microelectrophoretically near cell bodies and/or in the substantia gelatinosa (SG) of the rat spinal cord, on the response of neurones of laminae 4 and 5 to noxious and innocuous skin stimuli. NA was relatively selective in reducing nociceptive responses, but produced no or little effect on non-nociceptive responses. While 5-HT also reduced nociceptive responses, selective reduction occurred less frequently than with NA. Amino acids administered into the SG had little or no effect on neuronal responses. Gamma-aminobutyric acid failed to mimic the actions of the monoamines, suggesting that selective reduction of nociceptive responses cannot be explained by postsynaptic depression of lamina 2 neurones. The failure of naloxone to antagnoize the effects of NA and 5-HT ejected in the SG suggests that analgesia induced by stimulation of brainstem raphe nuclei does not involve the release of an endorphine in the SG. The selective reduction of nociceptive responses of dorsal horn neurones by NA and 5-HT may be relevant to the analgesia induced by stimulation of brainstem nuclei which contain the cells of origin of descending NA and 5-HT containing fibers. 15 references.

002247 Hodge, Gordon Karl. UCLA, Los Angeles, CA 90024 **Analysis of the role played by the substantia nigra in the mediation of ingestive, locomotor, and rotational behaviors as revealed by surgical and pharmacological manipulations. (Ph.D. dissertation).** Dissertation Abstracts International. Ann Arbor, MI, Univ. M-films, No. 77-17229 HC$15.00 MF$7.50 177 p.

A study to further extend the precision by which brain mechanisms underlying ingestive, locomotor, and rotational behaviors are elucidated is presented, focusing on the role the substantia nigra serves in the control of these activities. Female rats received either bilateral or unilateral radiofrequency or 6-hydroxydopamine (6-OHDA) lesions in the areas of the substantia nigra or median raphe. Baseline and postoperative food and water intakes, bodyweights, and photocell locomotor activities were recorded over periods as long as 6 months. Dextramphetamine, apomorphine, and pimozide were injected, and effects on locomotor activity was observed. Neither aphagia nor adipsia were found consequent to radiofrequency lesions of pars compacta of the substantia nigra. Most lesions destroyed virtually all compacta neurons with some or very little discernible damage to adjoining areas. 6-OHDA impaired ingestive behaviors but there was no compelling correlation between the extent of compacta damage and the degree of behavioral impairment. Injury of other structures, particularly those regions located in the tegmentum lateral to the red nucleus, seemed most important in determining the degree of ingestive disorders. Rats with bilateral compacta lesions were chronically hyperactive. The intensity and duration of hyperactivity were correlated with the degree of selective compacta destruction. Dextramphetamine and apomorphine were without effect, whereas pimozide reduced activity. The data indicate that the pars compacta did not play a critical role in the control of food and water intakes, but was of importance in the regulation of locomotor activity in the rat. The asymmetries displayed by rats with unilateral lesions in and around the substantia nigra varied considerably. The degree of spontaneous contralateral turning evinced by rats with lesions of pars compacta seemed related to the extent of compacta damage, but responses to drugs did not appear related to the extent of damage. The data reveal that relatively small differences in lesions can result in significant differences in behaviors, indicating a need for reserve in data interpretation and theoretical formulation. It is suggested that the present practice where histological verification and documentation receive little attention will impede understanding of brain organization and function by obscuring the more subtle and intricate processes underlying behavior. (Journal abstract modified)

002248 Holman, R. Bruce; Elliott, Glen R.; Kramer, Andrew M.; Seagraves, Eli; Barchas, Jack D. Nancy Pritzker Laboratory of Behavioral Neurochemistry, Stanford University School of Medicine, Stanford, CA 94305 **Stereotypy and hyperactivity in rats receiving ethanol and a monoamine oxidase inhibitor.** Psychopharmacology (Berlin). 54(3):237-239, 1977.

The combined administration of tranylcypromine (TCP), a monoamine oxidase inhibitor, and ethanol to rats produced both a marked increase in general locomotion such as walking and running and the appearance of repetitive stereotyped head and trunk weaving, forepaw padding, and circling movements. Pretreatment with p-chlorophenylalanine (pCPA) abolished the stereotyped behaviors. In contrast, animals pretreated with alpha-methyl-p-tyrosine (AMPT) were virtually indistinguishable from those receiving only TCP plus ethanol, except for a decrease in running behaviors. The above results are consistent with a serotonergic mediation of these specific stereotypies. The mechanisms by which TCP plus ethanol might produce these effects are discussed. 8 references. (Author abstract modified)

002249 Hunt, G. P.; Overstreet, D. H. School of Biological Sciences, Flinders University of South Australia, Bedford Park, S. Australia 5042, Australia **Evidence for parallel development of tolerance to the hyperactivating and discoordinating effects of ethanol.** Psychopharmacology (Berlin). 55(1):75-81, 1977.

To determine the possibility of parallel development of tolerance to the hyperactivating and discoordinating effects of ethanol, rats maintained on diets containing 6.5% ethanol or equicaloric sucrose solutions were challenged at weekly intervals with 1.5or 2.0g/kg ethanol or isotonic saline 14 hr after withdrawal from the diet. Tolerance developed to both the hyperactivating and discoordinating effects of the 1.5g/kg dose, but was less obvious with the 2.0g/kg dose. Chlorpromazine (2.5mg/kg) had a greater depressant effect in animals chronically treated with ethanol, suggesting that some alterations in the functioning of noradrenergic and/or dopaminergic systems may accompany chronic ethanol treatment. However, amphetamine and propranolol did not appear to affect ethanol and sucrose-treated rats differently. Results indicate a parallel development of tolerance to the discoordinating and hyperactivating effects of ethanol and implicate an underlying noradrenergic and/or dopaminergic mechanism, although the precise nature of the mechanism has not been clarified. 30 references. (Author abstract modified)

002250 Hymowitz, Norman; Brezenoff, Henry E. Department of Psychiatry and Mental Health Science, Behavioral Sciences Unit, New Jersey Medical School, 100 Bergen St., Newark, NJ 07103 **Effects of salsolinol, a tetrahydroisoquinoline alkaloid, on multiple schedule performance in rats.** Pharmacology Biochemistry and Behavior. 8(2):203-205, 1978.

To determine the effects of salsolinol, a tetrahydroisoquinoline derivative, on multiple schedule performance in rats, rats trained to lever press under a multiple fixed-ratio fixed-interval schedule of food reinforcement were given intracerebroventricular injections of 15 to 120 micrograms of salsolinol. Salsolinol caused a dose related decrease in fixed-ratio responding; however, fixed-interval responding was reduced only at the 120 microgram dose and was increased in two of

the animals after injection of 15 to 30 micrograms salsolinol. Further analysis of the behavioral effects of salsolinol is suggested. 18 references. (Author abstract modified)

002251 Johanson, Chris E. Dept. of Psychiatry, Univ. of Chicago, Chicago, IL 60637 **Effects of intravenous cocaine, diethylpropion, d-amphetamine and perphenazine on responding maintained by food delivery and shock avoidance in rhesus monkeys.** Journal of Pharmacology and Experimental Therapeutics. 204(1):118-129, 1978.

To test the effects of perphenazine, cocaine, diethylpropion and d-amphetamine on responding maintained by both food delivery and electric shock avoidance, a study was conducted using a multiple schedule of reinforcement in rhesus monkeys. This schedule had three components, each separated by a timeout: a fixed-ratio schedule of food delivery, a schedule of spaced responding (differential reinforcement of low rates) maintained by food delivery and a fixed-ratio schedule of shock avoidance. Control rates of responding on both ratio schedules were similar and were high relative to the low rates generated by the schedule of spaced responding. Perphenazine decreased rates on all three schedules in a dose dependent fashion. All three psychomotor stimulants decreased food maintained ratio responding at doses which had little effect on or increased rates of shock avoidance. Except for diethylpropion and d-amphetamine in one animal in which rates were increased, low rates of spaced responding were also decreased. It was concluded that the effects of the drugs were determined to some extent by the nature of the maintaining event. 32 references. (Author abstract)

002252 Johnson, David N. A. H. Robins Research Labs, Richmond, VA 23220 **Effect of diazepam on food consumption in rats.** Psychopharmacology (Berlin). 56(1):111-112, 1978.

To determine whether a reference antianxiety agent increases food consumption by attenuating emotional factors responsible for inhibition of food intake or by directly altering the mechanisms of hunger, the effect of diazepam on food consumption was evaluated in rats previously trained and untrained to milk consumption, and in a lever pressing task with or without negative reinforcement. Diazepam significantly increases milk consumption in rats that have never been exposed to this food before but not in rats trained to drink milk. Diazepam fails to increase lever pressing for food reward except when this behavior had been previously suppressed by the simultaneous administration of electric shock. These data suggest that diazepam does not alter appetite, but enhances the expression of motivation suppressed by instinct or training. 7 references. (Author abstract modified)

002253 Kariya, Tetsuhiko. Dept. of Neuropsychiatry, Faculty of Medicine, Tokyo Medical and Dental University, Tokyo 113, Japan **Manic-depressive illness and neurotransmitters.** Advances in Neurological Sciences (Tokyo). 21(4):714-723, 1977.

An investigation of the behavioral effects of administration of amine precursors and monoamine metabolism in rat brain with special attention to the neuropharmacological effects of antidepressants and lithium is presented along with a brief review of manic-depressive illness and neurotransmitters. Results indicated that intraperitoneal injections of iproniazid plus tetrabenazine in rats produced behavioral excitation, but injections of lithium every 12 hours had no effect on this behavioral excitation. The concentrations of lithium were significantly higher in each region of the brain of excited rats treated with iproniazid plus lithium. The effect of lithium on serotonin metabolism in the brain of rats under the monoamine altered conditions was different from the control rats. From these and other results, it was concluded that special attention should be paid to the monoamine altered conditions, which play an important role in the neurochemical effects of antidepressants and lithium in the brain. 41 references. (Author abstract modified)

002254 Katz, Jonathan L.; Barrett, James E. Dept. of Psychology, University of Maryland, College Park, MD 20742 **Ethanol, pentobarbital, and chlordiazepoxide effects in squirrel monkeys responding under fixed-ratio food presentation and stimulus-shock termination schedules.** Psychopharmacology (Berlin). 56(2):153-155, 1978.

Ethanol, pentobarbital, and chlordiazepoxide were administered to squirrel monkeys responding under a multiple schedule comprised of two fixed-ratio 100 response schedules (FR 100). Under one FR schedule, the one hundredth response produced food. Under the other schedule, the one hundredth response terminated the prevailing stimuli and accompanying schedule of electric shock presentation (stimulus/shock termination). Comparable high response rates were maintained under the two schedules. Each drug produced dose related decreases in response rates. With all three drugs the effects on all aspects of performance were quantitatively similar for both stimulus/shock termination and food maintained responding. Findings are taken to confirm the importance of schedule controlled rates and patterns of responding as significant determinants of drug effects. 11 references. (Author abstract modified)

002255 Katz, Jonathan L.; Barrett, James E. Dept. of Psychology, University of Maryland, College Park, MD 20742 **Effects of d-amphetamine and ethanol on responding of squirrel monkeys maintained under fixed-ratio schedules of food presentation and stimulus-shock termination.** Pharmacology Biochemistry and Behavior. 8(1):35-39, 1978.

Effects of d-amphetamine and ethanol were assessed on comparable behaviors maintained under fixed-ratio schedules of either food presentation or termination of electric shock and an accompanying visual stimulus. Ethanol affected the behaviors similarly in all important aspects; d-amphetamine increased rates of responding maintained by stimulus shock termination at doses that did not affect rates of food maintained responding. The increases in responding maintained by stimulus shock termination were not solely due to decreases in the pause prior to the initiation of responding. Results are discussed as regards previous findings which direct the interpretation of drug effects towards the actual environmental control of behavior. 15 references. (Author abstract modified)

002256 Katz, R. J.; Baldrighi, G.; Carroll, B. J. Mental Health Research Institute, Department of Psychiatry, University of Michigan Medical Center, Ann Arbor, MI 48109 **Effects of nomifensine (HOE 984) upon psychomotor activity and intracranial self-stimulation in the rat.** Pharmacology Biochemistry and Behavior. 7(3):269-272, 1977.

The effects of nomifensine maleate (HOE 984) were evaluated using two behavioral tasks to offer a preliminary assessment of the drug's potential psychostimulant properties. The drug produced dose related increase in both psychomotor activity and operant responding for brain stimulation reward. These results may point to possible psychostimulant properties for the drug. The animals tested were 32 adult male rats each maintained on ad lib food and water, and normal day/night cycles of 12 hr each. The animals were housed in groups of four. The clinical implications of the drug's antidepressant effects

and possible abuse potential are discussed. 24 references. (Author abstract modified)

002257 Kaymakcalan, Sukru; Ayhan, I. Hakki; Tulunay, F. Cankat. Dept. of Pharmacology, Ankara University Medical School, Sihhiye, Ankara, Turkey **Naloxone-induced or post-withdrawal abstinence signs in delta9-tetrahydrocannabinol-tolerant rats.** Psychopharmacology (Berlin). 55(3):243-249, 1977.

To investigate the occurrence of postwithdrawal or naloxone induced abstinence signs in delta9-tetrahydrocannabinol (THC) tolerant rats, 10 rats were injected s.c. with THC twice daily for 5 weeks in increasing doses, receiving 40mg/kg THC in each administration during the last 3 weeks. Ten control rats received the same amount of vehicle by the same route for the same period. The comparison of rectal temperatures of the first and fifteenth days showed that a very pronounced tolerance developed to the hypothermic effect of THC. The administration of naloxone on the 22nd and 31st days precipitated an opiate-like abstinence syndrome. The termination of the drug administration on the 35th day also produced a similar withdrawal syndrome. During abstinence, an increased locomotor activity was recorded by an activity meter. Similarly, the total amount of excreted feces and urine was higher in the THC group than in the controls. Both abstinence scores and increased motility exhibited the peak in the 48th h of withdrawal. It is concluded that the precipitation of an abstinence syndrome by a narcotic antagonist and the similarities of morphine and THC abstinence signs suggest some common features between cannabis and opiates. 32 references. (Author abstract modified)

002258 Kelly, P. H.; Moore, K. E. Dept. of Pharmacology, Michigan State University, East Lansing, MI 48824 **Mesolimbic dopamine neurons: effects of 6-hydroxydopamine-induced destruction and receptor blockade on drug-induced rotation of rats.** Psychopharmacology (Berlin). 55(1):35-41, 1977.

The role of the mesolimbic dopamine system in the drug induced rotation of rats with unilateral 6-hydroxydopamine (6-OHDA) lesions was examined. Bilateral injections of 6-OHDA into the nucleus accumbens greatly reduced the dopamine content of this nucleus and the olfactory tubercle and blocked the ipsilateral rotation induced by amphetamine and methamphetamine in rats with unilateral 6-OHDA lesions of the caudate nucleus. In contrast, apomorphine induced contralateral rotation was enhanced. Similar results were obtained when the destruction of forebrain noradrenergic neurons, normally produced by the nucleus accumbens 6-OHDA lesion, was prevented by desipramine (DMI) pretreatment. Microinjections of the dopamine receptor antagonist haloperidol into the nucleus accumbens did not spread to the olfactory tubercle, as assessed by the distribution of (3H)haloperidol, and blocked circling induced by amphetamine and apomorphine. Amphetamine induced circling was less effectively blocked by haloperidol injected into the olfactory tubercle. These results suggest that activity at nucleus accumbens dopamine receptors can greatly affect circling behavior, perhaps by amplifying asymmetries of nigrostriatal activity. 37 references. (Author abstract modified)

002259 Klawans, Harold L.; D'Amico, Donald J.; Nausieda, Paul A.; Weiner, William J. Dept. of Pharmacology, Rush-Presbyterian-St. Lukes Medical Ctr., Chicago, IL **The specificity of neuroleptic- and methysergide-induced behavioral hypersensitivity.** Psychopharmacology (Berlin). 55(1):49-52, 1977.

To determine whether hypersensitivity induced by a chronic dopamine antagonist (chlorpromazine or haloperidol) and by a serotonin antagonist (methysergide) is specific to their respective agonists or whether the induced physiologic alterations are more generalized, chlorpromazine, haloperidol, or methysergide was given to guinea-pigs daily for 21 days and the subsequent behavioral responses to d-amphetamine, apomorphine, and D,L-5-hydroxytryptophan were observed. Chronic dopaminergic antagonism resulted in hypersensitivity to dopamine agonism but did not change the response to serotonin agonism as gauged by 5-hydroxytryptophan induced stereotypy. Chronic serotonin antagonism was shown to result in hyper- sensitivity to serotonin agonism, which was not associated with any increase in the behavioral response to either direct or indirect dopamine antagonists. These findings indicate that the chronic administration of dopamine and serotonin antagonists results in behavioral hypersensitivity, which is limited to the system antagonized, and that antagonist induced hypersensitivity involves the transmitter specific receptors blocked by the antagonist in question. 11 references. (Author abstract modified)

002260 Knowles, W. D.; Phillips, M. Ian. Neurobehavior Laboratory, Department of Physiology, University of Iowa, Iowa City, IA 52242 **Effects of anesthetics on cerebellar neurons recorded chronically after harmaline.** Federation Proceedings. 36(3):353, 1977.

Effects of various anesthetics and harmaline on tremor and bursting patterns of neurons in rats chronically implanted with electrodes in the cerebellar cortex will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Rats were injected i.p. with harmaline and bursting neural activity and tremor were recorded. Rats were then anesthetized with a variety of agents. Inhalation of ether and 12% ethanol by gastric intubation blocked tremor and bursting. Pentobarbital, chloral hydrate, and dial with urethane slowed the rate of bursting and caused it to become intermittent. Tremor could be blocked while tremor was still occurring, bursting could become intermittent or was blocked completely, and bursting could be slowed without becoming intermittent. (Journal abstract modified)

002261 Kokkinidis, L.; Anisman, H. Dept. of Psychology, Carleton University, Ottawa, Ontario, Canada **Behavioural specific tolerance following chronic d- or l-amphetamine treatment: lack of involvement of p-hydroxynorephedrine.** Neuropharmacology (Oxford). 17(2):95-102, 1978.

To further explore behavioral specific tolerance to chronic administration of d-amphetamine or l-amphetamine and to examine the possible involvement of p-hydroxynorephedrine, a series of studies were undertaken in Swiss-Webster mice. In a free-running Y-maze exploratory task mice tend to enter the least recently visited compartment (spontaneous alternation). Treatment with d-amphetamine or l-amphetamine produced a dose dependent increase in locomotor activity and resulted in animals successively exploring two compartments of the Y-maze only (perseveration). Whereas five daily injections of d-amphetamine (10mg/kg) or l-amphetamine (45mg/kg) did not result in tolerance to the locomotor stimulating properties of the drug, a dose dependent attenuation of the perseverative tendency was observed. Moreover, symmetrical cross-tolerance between the isomers was apparent. Since formation of p-hydroxynorephedrine is stereospecific to the d-isomer, these data suggest that this possible false transmitter does not play a primary role in the development of the tolerance. Alternative explanations which may account for the behavior

specific tolerance are considered. 33 references. (Author abstract modified)

002262 Koob, George F.; Del Fiacco, Marina; Iversen, Susan D. Arthur V. Davis Center for Behavioral Neurobiology, Salk Institute, P.O. Box 1809, San Diego, CA 92112 **Spontaneous and amphetamine-induced behavior after bilateral injection of ethanolamine-O-sulfate into the substantia nigra.** Brain Research (Amsterdam). 146(2):313-323, 1978.

A series of experiments was undertaken to examine spontaneous and amphetamine induced behavior and gamma-aminobutyric acid (GABA) effects of ethanolamine-O-sulfate (EOS) into the zona reticulata of the substantia nigra (SN) in rats. Injection produced immediate contraversive turning. Bilateral injections produced spontaneous stereotyped behaviors including sniffing and biting. After 24 hours, rats showed a significantly decreased locomotor response to d-amphetamine. The spontaneous behaviors elicited following the initial injection of EOS increased both in nature and duration with the second and third injections of EOS, and persevered for 24 h. At this time, d-amphetamine intensified this spontaneous stereotyped behavior. GABA levels were significantly higher in SN, hypothalamus, corpus striatum and cerebral cortex 24 h following single or repeated injections of EOS. Dopamine levels in the corpus striatum were unchanged 24 h following the EOS treatment except by the injection procedure itself. Control injections into the thalamus produced no turning or stereotypy, nor an enhanced response to d-amphetamine. GABA levels were, however, significantly higher in SN and thalamus 24 h following repeated injections of EOS into the thalamus. Results are consistent with the hypothesis that GABA containing neurons comprise part of the efferent output of the corpus striatum and do not act exclusively through a dopaminergic substrate. 24 references. (Author abstract modified)

002263 Korol, Bernard; Yaffe, G. J.; Biddy, R. L.; Bidus, D. R. Dept. of Psychiatry, St. Louis University, St. Louis, MO 63125 **A behavioral and autonomic nervous system study of chronic imipramine administration to conscious dogs.** Pharmacology (Basel). 16(2):61-69, 1978.

In a behavioral and autonomic nervous sytem study of chronic imipramine administration to conscious dogs, the clinically effective antidepressant imipramine, an iminodibenzyl structure, was examined in two experimental methods which had previously demonstrated high prediction ability in discerning and categorizing potential psychotherapeutic drugs. The chronic administration of imipramine produced a significant reduction in the scores of aberrant behavioral response evoked by the fixed dose with Ditran seen as early as 1 week after treatment was initiated and continuing through the 8 week treatment duration. This chronic oral treatment with impramine was also associated with a significant potentiation of mean arterial pressure responses to fixed dose treatment with serotonin, noradrenaline, yohimbine and adrenaline, while significantly inhibiting the histamine induced depressor response. The results support the speculation that, in dogs, the clinically effective antidepressants antagonize or reverse the Ditran induced response and produce an associated response of sympathetic nervous system arousal or sensitization. 20 references. (Author abstract modified)

002264 Kovacic, Beverly; Wang Lu, Lee-Jane; Ruffing, Diane; Domino, Edward F. Lafayette Clinic, Dept. of Pharmacology, 951 E. Lafayette, Detroit, MI 48207 **Interactions of partial LSD analogs with behavioral disrupting effects of LSD and DMT in the rat.** European Journal of Pharmacology (Amsterdam). 47(1):37-44, 1978.

Interactions of partial LSD analogs with behavioral disrupting effects of LSD and N,N-dimethyltryptamine (DMT) were investigated in the rat. Adult rats were trained to barpress on a schedule whereby every fourth press earned a reward of 0.01ml of sugar sweetened milk. After an i.p. injection of LSD (0.1mg/kg) or DMT (3.2or 10mg/kg) such barpressing is abolished completely and resumed usually within an hour, at a rate near the preinjection control rate of pressing. It continues at a steady, uninterrupted pace until the animals are removed from the operant chamber one half hour later. A series of N,N-diethylnipecotamide derivatives, N,N-diethylbutyramide and 1-methyl-1,2,5,6-tetrahydropyridine-3-(N,N-diethylcarboximide), were also tested. Pretreatment with a single i.p. injection of any of these compounds (5 to 40mg/kg) either had no effect on or else prolonged the duration of hallucinogen induced cessation of barpressing. 11 references. (Author abstract modified)

002265 Krimmer, Edward C.; Barry, Herbert, III. School of Pharmacy, University of Pittsburgh, Pittsburgh, PA **Attributes of discriminative pentobarbital stimulus immediately after intravenous injection.** In: Ho, B., Drug Discrimination and State Dependent Learning. New York, Academic Press, 1978. 392 p. (p. 175-190).

Research findings for discrimination learning using pentobarbital are reviewed, and a study in rats using a novel learning technique in which the discrimination consisted of differential active and passive shock avoidance responses in a two compartment box is reported. The procedures described were developed to investigate the discriminable properties of pentobarbital immediately after intravenous (IV) administration and to compare this immediate effect with the discriminable effect of the drug as tested at longer time intervals following intraperitoneal (IP) injection. It was shown that the IV route of administration and short onset testing interval are effective conditions for discriminative learning with pentobarbital in the rat. The results revealed that the discriminative properties of the drug are qualitatively similar for the IV and IP routes but differ quantitatively. It is suggested that the advantages of the IV route (lower doses, shorter time intervals) are outweighed by the disadvantages (the need for surgical intervention and the presence of nonfunctional cannulas throughout the study). Studies concerning the specificity or generality of the pentobarbital discriminative response with other hypnotic drugs are reviewed, and the theoretical implications of the present study are discussed. 25 references.

002266 Ksir, Charles J., Jr. University of Wyoming, Laramie, WY **Rate-dependent and stimulus control effect of drugs.** Psychopharmacology Bulletin. 14(1):66-67, 1978.

A summary of an ongoing research project on the relationship between the effectiveness of a given drug in altering a particular behavior and the rate of occurrence of that behavior in relation to other activities, and the relationship between drug effectiveness and stimulus control of behavior is presented. In a study to evaluate the effects of LSD and amphetamine on fixed-interval responding, stable performance is established in the drug state, and the effect of saline substitution is observed. Initial results indicate that a drug which is a discriminative stimulus need not disrupt responding, since not all discriminative stimuli are sufficiently compelling to produce such a disruption.

002267 Kubicki, Jan. Zaklad Fizjologii Instytutu Fizjologii i Biochemii AM, Lindleya 3, 90-131 Lodz, Poland. **Some behavioral effects of SP6-11 hexapeptide C-terminal of substance P injected into the cerebral ventricles in rats.** Acta Physiologica Polonica (Warszawa). 28(5):489-492, 1977.

The effects of the peptide SP6-11 injected into the lateral brain ventricle in chronic rats on the alimentary behavior in a maze and on spontaneous exploratory reactions were studied. It was found that the peptide SP6-11, in doses ranging from 50 to 500pmol, increased only locomotor activity and did not change a number of correct trials in a maze. 22 references. (Author abstract)

002268 Leander, J. David; McMillan, Donald E. Dept. of Pharmacology, School of Medicine, University of North Carolina, Chapel Hill, NC 27514 **Mazindol effects on schedule-controlled responding of the pigeon.** European Journal of Pharmacology (Amsterdam). 48(1):11-17, 1978.

The effects of mazindol, a nonphenethylamine anorexic, were determined in pigeons key pecking under a multiple fixed-ratio 30 response, fixed-interval 5 min schedule of food presentation. The low average rates of responding under the fixed-interval schedule were greatly increased (from 0.7response/sec to 2 responses/sec) at doses from 0.1to 10mg/kg. The higher rates of responding under the fixed-ratio schedule were only decreased by increasing doses of mazindol. Throughout the fixed interval, mazindol tended to produce a constant rate of responding completely disrupting the normal, positively accelerated pattern of responding. These rate increasing effects of mazindol were much greater than those of phenethylamines tested under similar conditions. The large increases in rates of responding under the fixed-interval component are discussed in terms of the known biochemical effects of mazindol. 24 references. (Author abstract)

002269 Lee, H. K.; Chai, C. Y.; Wayner, M. J.; Hsu, C. H.; Chung, P. M. Dept. of Biophysics, National Defense Medical Ctr., PO Box 8244, Taipei, Taiwan **Morphine-induced tail erection: site of action.** Pharmacology Biochemistry and Behavior. 8(1):69-73, 1978.

Acute ablation techniques were used to determine the site of action of morphine induced tail erection (MITE) within the central nervous system of mice. Morphine produced no elevation of tails in mice whose spinal cord had been transected at the lower thoracic or lumbar levels. Decortication and high level precollicular decerebration did not prevent MITE while morphine caused no tail response at all in low level inferior collicular decerebrate mice. Lesions in various portions of the mesencephalon revealed that the degree of MITE was closely related to the size of the lesions of the central gray matter. The larger the lesion, the smaller the degree of tail elevation. MITE could not be elicited in mice when the mesencephalic central gray matter had been completely destroyed. Results indicate that morphine acts on the mesencephalic central gray matter producing tail erection and the pathway responsible for the reaction descends from the midbrain downward to the spinal cord. 11 references. (Author abstract)

002270 Leibowitz, Sarah F. Rockefeller University, New York, NY **Central drug and lesion studies of feeding.** Psychopharmacology Bulletin. 14(1):67, 1978.

A summary of an ongoing research project on central drug and lesion studies of feeding behavior is presented. The effects of centrally administered drugs (amphetamine and other releasers of catecholamines, adrenergic agonists, adrenergic blockers, and inhibitors of catecholamine inactivation) on the alpha-adrenergic and beta-adrenergic mechanisms controlling feeding behavior are being studied. Goals of the research are: 1) to determine if catecholamine releasing drugs can produce the same localized pattern of feeding effects produced by direct adrenergic stimulation of the diencephalon; 2) to study the specific norepinephrine pathways that innervate the diencephalon in terms of their function in the regulation of natural feeding behavior; and, 3) to examine the functional relationship between the different norepinephrine pathways innervating specific diencephalic regions and the adrenergic receptor feeding systems localized in these regions.

002271 Liljequist, Sture; Ahlenius, Sven; Engel, Jorgen. Dept. of Pharmacology, University of Goteborg, Fack, S-40033 Goteborg, Sweden **The effect of chronic ethanol treatment on behaviour and central monoamines in the rat.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 300(3):205-216, 1977.

The effect of chronic ethanol treatment on the growth rate, diurnal pattern of drinking, open-field activity, and conditioned avoidance acquisition and retention were investigated in rats weaned at 16 days of age and treated with various ethanol concentrations for 270 days. Ethanol was found to induce reduction of bodyweight, increase in open-field activity, a slight difference in conditioned avoidance acquisition, and various degrees of hyperexcitability such as tremor, rigid body posture and convulsions. Termination of chronic ethanol resulted in two types of withdrawal syndromes: 1) an acute withdrawal syndrome observed 12 hr after termination, characterized by extreme hyperexcitability; and 2) a delayed withdrawal syndrome first occurring 3 days after termination, characterized by a more coordinated behavioral stimulation and increased tyrosine hydroxylation in the striatum and dopamine rich limbic structures. It is concluded that chronic ethanol administration induces various kinds of behavioral changes and that these changes are at least partly mediated via central catecholamine mechanisms. 62 references. (Author abstract modified)

002272 Lindquist, Mats P.; Gotestam, K. Gunnar. Psychiatric Research Center, University of Uppsala, Ulleraker Hospital, Uppsala, Sweden **Open-field behavior after intravenous amphetamine analogues in rats.** Psychopharmacology (Berlin). 55(2):129-133, 1977.

To evaluate the utility of an open-field technique for the study of rat behaviors, a variety of behaviors were studied in an open field setting after intravenous amphetamine, phenmetrazine, or fenfluramine. Amphetamine and phenmetrazine increase ambulation initially and rearing during the whole experiment, and decrease grooming. At 30 and 60 min, with the three higher (8 to 16mg/kg) doses of amphetamine, stereotyped behaviors interfere with and decrease both ambulation and grooming. Fenfluramine decreases ambulation, rearing, and grooming, and is the only drug to induce backing. The technique seems to be a simple and rapid method to establish dependence liability in amphetamine analogues. Interrater and test/retest reliability was established through ITV recordings. 23 references. (Author abstract modified)

002273 Lyubimov, B. I.; Ostrovskaya, G. Z. Laboratoriya obshchey farmakologii, Institut farmakologii AMN SSSR, Moscow, USSR /**Effect of psychotropic agents on the physical performance capacity of animals exposed to heat and cold.**/ Vliyanie psikhotropnykh veshchestv na fizicheskuyu rabotosposobnost' zhivotnykh v usloviyakh vysokoy i nizkoy

temperatury. Farmakologiya i Toksikologiya (Moskva). 40(2);133-136, 1977.

Effects of the psychostimulants benzedrine, caffeine, and sydnocarb on physical performance capacity of rats exposed to heat and cold were studied in white rats weighing 180g to 220g. The animals were placed in climate controlled boxes with the temperature set at 40 degrees to -10 degrees C for 1 hour periods. After 30 min various doses of the psychostimulants were administered. At the end of the hour the rats were subjected to the swimming test. It was ascertained that psychostimulants are capable of heightening the performance capacity of the animals: benzedrine in cooling, and caffeine and sydnocarb in overheating. Benzedrine increased performance capacity by 29.4%, caffeine by 21.0%, and sydnocarb 42.1%. 11 references.

002274 Makanjuola, R. O. A.; Hill, G.; Dow, R. C.; Campbell, G.; Ashcroft, G. W. MRC Brain Metabolism Unit, Univ. Dept. of Pharmacology, 1 George Sq., Edinburgh EH8 9JZ, Scotland **The effects of psychotropic drugs on exploratory and stereotyped behaviour of rats studied on a hole-board.** Psychopharmacology (Berlin). 55(1):67-73, 1977.

The effects of psychotropic drugs on exploratory and stereotyped behavior of rats on a hole board were examined. Increasing doses of dl-amphetamine stimulated both forms of behavior with stereotyped behavior becoming predominant particularly at the higher dose levels. At the highest dose of amphetamine used (16mg/kg) a gradual transition from exploratory to stereotyped behavior was observed with time. As the drug wore off this transition was reversed. Haloperidol at a dosage of 0.1and 0.05mg/kg blocked the response to a high dose of amphetamine whereas a lower dose (0.02mg/kg) blocked the stereotyped response to amphetamine while some exploratory behavior still took place. Apomorphine inhibited hole dipping but at lower doses another form of exploratory behavior was induced, this behavior becoming stereotyped as the dose was increased. It is concluded that there is a close relationship between exploratory and stereotyped behaviors, and that monoamine systems might play a significant role in the regulation of both forms. 24 references. (Author abstract modified)

002275 Malick, Jeffrey B.; Goldstein, Jeffrey M. Biomedical Research Department, Stuart Pharmaceuticals, Wilmington, DE 19897 **Analgesic activity of enkephalins following intracerebral administration in the rat.** Life Sciences (Oxford). 20(5):827-832, 1977.

Enkephalins were injected into a brain site sensitive to morphine to determine whether analgesia was produced. Male albino Wistar rats were implanted with cannuale in the dorsal border of the raphe nucleus in the midbrain periaqueductal gray. Either sterile water or drug was injected, and tail flick response to radiant heat was measured 1, 3, or 7 min later. Some rats were pretreated with naloxone. Sterile water showed no effect on tail flick. Morphine had a peak analgesic effect at 7 min, and the analgesia lasted several hours. Methionine enkephalin had a peak effect at 1 min, and its activity diminished at 7 min. Morphine was four times more potent than both enkephalins. Leucine enkephalin peaked in activity at 3 min, and decreased within 7 min. Naloxone failed to alter response latencies by itself, but inhibited the analgesic activity of morphine, methionine enkephalin, and leucine enkephalin. 19 references.

002276 Malila, Aino. Research Laboratories of the State Alcohol Monopoly, Box 350, SF-00101, Helsinki 10, Finland **Intoxicating effects of three aliphatic alcohols and barbital on two rat strains genetically selected for their ethanol intake.** Pharmacology Biochemistry and Behavior. 8(2):197-201, 1978.

Intoxicating effects of ethanol, isopropanol, tert. butanol and barbital were studied by comparing performances on the tilted plane of ethanol preferring (AA) and ethanol avoiding (ANA) rat strains raised by genetic selection for their voluntary ethanol intake. The motor coordination of AA rats were found to be less affected than that of ANA rats by all three alcohols and barbital. A marked genetic difference in neural tolerance to the alcohols and barbital is indicated, and it is suggested that neural tolerance to alcohols plays a role in determining the ethanol preference of AA rats and ethanol aversion of ANA rats. 33 references. (Author abstract)

002277 Maroli, Allan N.; Tsang, Wah-Kwan; Stutz, Robert M. Department of Psychology, University of Cincinnati, Cincinnati, OH 45221 **Morphine and self-stimulation: evidence for action on a common neural substrate.** Pharmacology Biochemistry and Behavior. 8(2):119-123, 1978.

To determine whether the self-stimulation phenomenon may provide a useful technique for investigating the rewarding properties of potentially addictive drugs such as morphine, the nature of morphine's effects on self-stimulation was examined by observing changes in rate intensity functions following morphine administration. The results indicate that morphine markedly enhanced bar-pressing for low intensity stimulation when the intensities were presented in an ascending sequence but produced only slight changes in self-stimulation rates when a descending series was used. The failure of morphine to facilitate responding in the descending series suggests that adaptation of the self-stimulation system can block morphine's effects on this system. Findings appear to support the hypothesis that morphine affects the excitability of the neural system which mediates self-stimulation. 24 references. (Author abstract)

002278 Marshall, John F. Department of Psychobiology, University of California, Irvine, CA 92717 **Resistance of alloxan-diabetic rats to the behavioral activation induced by d-amphetamine: partial restoration with a high fat/protein diet.** Physiology & Behavior. 20(3):319-322, 1978.

To examine the effects of dietary manipulations on the resistance to behavioral effects of d-amphetamine found in diabetic rats, alloxan induced diabetic rats were fed on a high carbohydrate or high fat/protein diet for 6 weeks and locomotor and stereotypic behaviors were rated. Results indicate that whereas alloxan injected rats maintained on a high carbohydrate diet show predominantly increased forward locomotion and weak stereotyped sniffing following 2.0mg/kg d-amphetamine sulfate, this same dose typically induces moderately intense stereotyped sniffing in alloxan injected rats which have ingested a high fat/protein diet for 6 weeks. The strength of the behavioral activation produced by d-amphetamine in non diabetic control rats is not influenced by whether they ingest a high carbohydrate or high fat/protein diet, and is significantly greater than the behavioral activation seen in diabetics maintained on high carbohydrate diet, but does not differ significantly from the degree of behavioral activation seen in diabetic rats maintained for 6 weeks on a high fat/protein diet. Thus, it appears that the ingestion of a high fat/protein diet ameliorates the hyperglycemia and hyperdipsia and facilitates the weight gain of the diabetic animal, it is suggested that this diet restores the responsiveness of alloxan injected rats to d-amphetamine by partially correcting the metabolic deficiencies associted with the diabetic state. 18 references. (Author abstract modified)

002279 Mason, Stephen T.; Sanberg, Paul R.; Fibiger, Hans C. Div. of Neurological Sciences, Dept. of Psychiatry, University of British Columbia, Vancouver, B.C. V6T 1W5, Canada **Amphetamine-induced locomotor activity and stereotypy after kainic acid lesions of the striatum.** Life Sciences (Oxford). 22(6):451-459, 1978.

The effects of kainic acid lesions on amphetamine induced locomotor activity and stereotypy were studied to further evaluate the putative kainic acid animal model for Huntington's disease and other disease states in humans. Kainic acid injections were used to destroy cell bodies in the striatum without affecting afferent terminals or fibers of passage. Substantial decreases in choline acetyltransferase and glutamic acid decarboxylase were found particularly in the dorsal half of the striatum but no alteration in the marker enzyme for dopamine terminals, tyrosine hydroxylase. The locomotor and stereotypical effects of d-amphetamine were tested in these animals and a marked and consistent increase in the effects of amphetamine was found on both measures. This is interpreted in terms of a disruption of the striatonigral feedback system and as suggesting a possible dissociation of function within the striatum between the dorsal and the ventral parts. 49 references. (Author abstract modified)

002280 McKenna, Mary; Ho, Beng T. Texas Research Institute of Mental Sciences, 1300 Moursund Ave, Houston, TX 77030 **Induced tolerance to the discriminative stimulus properties of cocaine.** Pharmacology Biochemistry and Behavior. 7(3):273-276, 1977.

The effects of repeated administration of cocaine for the development of tolerance or supersensitivity in rats using drug discrimination on the performance measured were examined. Twenty-five male Sprague-Dawley rats were trained in five two-lever operant chambers on a DRL-15 sec schedule of positive food reinforcement to discriminate 10 mg/kg cocaine from 1 ml/kg saline. Following acquisition of discrimination a counterbalanced design of extinction tests was performed before and after repeated administration of 20 mg/kg cocaine or saline (three times a day at 5 hr intervals for 7 days. The extinction tests consisted of testing responses of animals following difference in animals' lever choice before and after repeated injection with saline. However, the percent cocaine lever choice with the two doses of cocaine was lower after repeated administration of cocaine than before the repeated injections. This indicates tolerance developed to the discriminative stimulus properties of cocaine. 24 references. (Author abstract modified)

002281 Meisch, Richard A., Stark, Linda J. Psychiatry Research Unit, Mayo Box 392, University of Minnesota, Minneapolis, MN 55455 **Establishment of etonitazene as a reinforcer for rats by use of schedule-induced drinking.** Pharmacology Biochemistry and Behavior. 7(3):195-203, 1977.

Drinking of etonitazene HC by six rats was studied during daily 4 hour sessions. Five related experiments were conducted sequentially. In the first experiment schedule induced polydipsia was established. Subsequently, etonitazene concentrations (1.25, 2.5and 5.0microgram/ml) were substituted for water, and intake of large quantities of the drug occurred. In the second experiment the concurrent food reinforcement schedule was discontinued and lever presses maintained by etonitazene persisted. In the third experiment the number of lever presses required per dipper presentation of etonitazene was increased, and rate of lever pressing increased directly with the reponse requirement whereas number of dipper presentations remained constant. In the fourth experiment water was substituted for the 5 microgram/ml etonitazene solution. Water responding declined to low rates, but when etonitazene was reintroduced, responding increased to previous levels. Thus, etonitazene was functioning as a positive reinforcer. In the final experiment, progressive increases in the etonitazene concentration resulted in both systematic decreases in response rate and increases in quantity consumed. 21 references. (Author abstract)

002282 Messiha, F. S. Department of Pharmacology and Therapeutics, Texas Tech University, School of Medicine, Lubbock, TX 79409 **Amantadine hydrochloride (AMN): antagonism to ethanol (ETOH)-mediated responses in rodents.** Federation Proceedings. 36(3):285, 1977.

Because of the implication of a dopaminergic mechanism in the pharmacological actions of amantadine and ethanol, the effect of amantadine on certain ethanol evoked responses in the mouse and rat was studied. Results will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Administration of amantadine prior to ethanol decreased the central depressant action of alcohol as measured by the duration of alcohol produced narcosis in mice. Amantadine markedly reduced voluntary intake of ethanol by the rat for the 24 hr period following drug injection. Amantadine did not inhibit cytoplasmic liver alcohol dehydrogenase or mitochondrial aldehyde dehydrogenase activities in vivo in rats when given daily for 7 days, but it did inhibit the enzymes in vitro by 38% and 42%, respectively. Amantadine may be useful in treating alcoholism if it is devoid of a disulfiram-like reaction. (Journal abstract modified)

002283 Meyer, D. R.; El-Azhary, R.; Bierer, D. WS.; Hanson, S. K.; Robbins, M. S.; Sparber S. B. Department of Pharmacology, University of Minnesota, Minneapolis, MN 55455 **Tolerance and dependence after chronic administration of clonidine to the rat.** Pharmacology Biochemistry and Behavior. 7(3):227-231, 1977.

In a study of the effect of clonidine upon operant behavior, it was determined that acute administration of clonidine (10 to 70 microgram/Kg, IP disrupted operant behavior in rats maintained by a fixed-ratio schedule of reinforcement. When chronically administered (100 microgram Kg, IP and 3 microgram S/ML in drinking water) tolerance to the behavioral depressant effect developed within a few days and was complete by 14 days. Abrupt termination of drug treatment in tolerant rats resulted in an abstinence reaction which was characterized by suppression of operant performance for as long as 1 week. These results demonstrated the development of tolerance to and dependence on clonidine in rats. These behavioral observations in rats may be related to rebound hypertension and irritability of patients given this adrenergic agonist for treatment of hypertension. 12 references. (Author abstract modified)

002284 Monti, Jaime M. Dept. de Psicobiologia, Escola Paulista de Medicina, Sao Paulo, Brazil **Hypnotic-like effects of cannabidiol in the rat.** Psychopharmacology (Berlin). 55(3):263-265, 1977.

The effects of cannabidiol (CBD), a cannabis constituent, on the sleep-wakefulness cycle of male Wistar rats were assessed. During acute experiments, single doses of 20mg/kg CBD decreased slow wave sleep (SWS) latency. After 40mg/kg SWS time was significantly increased while wakefulness was decreased. REM sleep was not significantly modified. Following the once daily injections of 40mg/kg CBD for a period of 15 days, tolerance developed to all the above mentioned ef-

fects. Results are taken to indicate that cannabidiol behaves as a short acting hypnotic in the rat. 8 references. (Author abstract modified)

002285 Morley, Barbara J.; Worsham, Elizabeth. Neurosciences Program, University of Alabama Medical School, Birmingham, AL 35294 **The effects of prolonged handling, scopolamine, and physostigmine on the activity of isolated and socially reared rats.** Physiological Psychology. 6(1):83-88, 1978.

Effects of prolonged handling, scopolamine, and physostigmine on the activity of isolated and socially reared rats were studied. Sprague-Dawley albino rats were reared in one of three social environments: isolation, low density, or high density. Baseline activity, measured by photobeam crossings in a 15 min session, was assessed for 16 consecutive days. The response to 1 and 10mg/kg of scopolamine and .05 and .1mg/kg of physostigmine was then assessed. It was found that isolated animals were more active than socially reared animals, and that this isolation induced increased activity was not eliminated with repeated handling and behavioral testing. The activity of the animals in a low density of group was not significantly greater than that of animals raised in a high density group. Scopolamine and physostigmine were both found to decrease activity, but there was not a differential effect of the drugs on animals raised in the three social environments. It was concluded that tactile stimulation does not alter the effects of isolation rearing and that a baseline activity level can be established for the investigation of the physiological bases of the behavioral effects of isolation rearing. 26 references. (Author abstract)

002286 Murray, T. F.; Craigmill, A. L.; Fischer, G. J. Dept. of Psychology, School of Medicine, SJ-30, University of Washington, Seattle, WA 98195 **Pharmacological and behavioral components of tolerance to LSD and mescaline in rats.** Pharmacology Biochemistry and Behavior. 7(3):239-244, 1977.

The relative contributions of pharmacological and behavioral mechanisms in the development of tolerance to the disruptive effects of LSD and mescaline in rats responding to a fixed-ratio of water reinforcement (FR-10) were examined. Rats treated daily with LSD or mescaline before operant testing developed tolerance to the impairment of responding, while rats treated daily after each session did not display tolerance when the drugs were administered before testing. These results indicate that behavioral compensatory mechanisms may be involved in the development of tolerance to the disruptive effects of LSD and mescaline on fixed-ratio (FR-10) performance. 15 references. (Author abstract modified)

002287 Nandy, K. Education and Clinical Center, Veterans Administration Hospital, 200 Spring Road, Bedford, MA 01730 **Centrophenoxine: effects on aging mammalian brain.** Journal of the American Geriatrics Society. 26(2):74-81, 1978.

The effects of centrophenoxine on the learning and memory of old mice were investigated. The results were correlated with changes in neuronal lipofuscin in the cerebral cortex and hippocampus. Old female mice (11 or 12 months) were treated with centrophenoxine for three months and their learning and memory were tested in a T-maze. The number of trials required to attain the criterion in the 20 treated old mice were compared with those for 20 untreated mice of the same age and for 20 younger untreated mice. The treated animals learned the task with significantly fewer trials, and also exhibited a reduction of neuronal lipofuscin pigment in both the cerebral cortex and the hippocampus. The changes in lipofuscin were demonstrated by study of the characteristic autofluorescence, and by histochemical and ultrastructural (electron microscope) observations. 44 references. (Author abstract modified)

002288 Nowak, Jerzy Z. Zaklad Amin Biogennych, Inst. Farmakologii PAN, Narutowicza 60, 90-136 Lodz, Poland **The influence of histamine on metabolism of dopamine and serotonin in the rat striatum.** Acta Physiologica Polonica (Warszawa). 28(2):101-105, 1977.

A study of the influence of histamine on metabolism of dopamine and serotonin in the rat striatum is presented. Histamine-2HCl (Hi) given in a dose of 500 micrograms did not change DA level in the striatum but HVA was increased by approximately 50%. The Hi induced rise of HVA level was prevented in animals pretreated with an antihistaminic drug -- mepyramine. The pretreatment of rats with atropine reduced significantly the Hi induced rise of HVA concentration. Hi did not signinficantly ifluence 5-HT content in the striatum while the level of 5-HIAA was simultaneously increased by 15%. It is concluded that Hi induced elevation of HVA content is not a direct effect of Hi on dopaminergic neurons but the Hi action is exerted indirectly through cholinergic system. The increase of serotonergic activity is probably a consequence of an increased activity of dopaminergic neurons in the striatum. 20 references. (Journal abstract modified)

002289 Nozaki, M.; Bell, J. A.; Vaupel, D. B.; Martin, W. R. NIDA, Div. of Research, Addiction Research Ctr., Lexington, KY 40511 **Responses of the flexor reflex to LSD, tryptamine, 5-hydroxytryptophan, methoxamine, and d-amphetamine in acute and chronic spinal rats.** Psychopharmacology (Berlin). 55(1):13-18, 1977.

The flexor reflex of acute (40 to 48 hr after mid-thoracic spinal transection) and chronic (at least 2 months after transection) spinal rats was evoked by tetanic electrical stimulation of both hindfeet and recorded on a polygraph using a transducer connected to the left hindfoot to study effects of LSD, d-amphetamine, methoxazine, 5-hydroxytryptophan (5-HTP) and tryptamine on the flexor reflex. The flexor reflex in the chronic spinal rat was more responsive to electrical stimulation and to the actions of drugs studied than was the flexor reflex in the acute spinal rat. In chronic spinal rats, d-amphetamine, methoxamine, LSD, tryptamine, and 5-HTP facilitated the flexor reflex and induced spontaneous movements. These facilitative effects were seen in acute spinal rats only when much larger i.p. doses of amphetamine, methoxamine, and LSD were used. Small i.v. doses of tryptamine also produced the facilitation. The facilitation caused by LSD and tryptamine, but not 5-HTP, in chronic spinal rats was antagonized by cyproheptadine. These observations suggest that chronic spinal rats were more sensitive to the drugs than acute spinal rats and support the hypothesis that the mode of action of LSD is similar to that of tryptamine but different from that of 5-HTP since cyproheptadine antagonized the facilitative effects of LSD and tryptamine but not those of 5-HTP. 28 references. (Author abstract)

002290 Oka, Makoto; Kamei, Chiaki; Shimizu, Masanao. Dept. of Pharmacology, Research Lab., Dainippon Pharmaceutical Co., Ltd., Suita shi, Osaka 564, Japan **Effect of neuroleptic drugs on the conditioned behavior after pretreatment with alpha-methyltyrosine or p-chlorophenylalanine.** Japanese Journal of Pharmacology (Kyoto). 27(6):807-815, 1977.

Effects of psychotropic drugs on conditioned behavior after pretreatment with alpha-methyltyrosine (alpha-MT) or p-

chlorophenylalanine (PCPA) were studied using operant conditioning technique in rodents. The operant conditioning procedure used was composed of a concurrent milk reinforced and avoidance schedule in an operant conditioning chamber with two levers where lever pressing by rats was maintained by milk (VR-6) and electric shock (intertrial interval 1 min). Chlorpromazine, perphenazine, haloperidol, and oxypertine, at half of the maximum ineffective dose, respectively, caused a significant decrease in both lever pressings after pretreatment with alpha-MT. Such potentiating effect by alph-MT was not observed with diazepam and nortriptyline. PCPA pretreatment did not influence suppressive effects on responding under both schedules by any drug used. The one-way active avoidance procedure in mice was also employed. On the avoidance response, chlorpromazine, perphenazine, haloperidol, trifluperidol, clozapine and oxypertine showed a suppressive effect, ED50 values of which were considerably lowered by pretreatment with alpha-MT. No influence was seen with PCPA. Diazepam, phenoxybenzamine, phentolamine, arecoline, physostigmine and clonidine also had a suppressive effect on the avoidance response, which was not influenced by pretreatment with alpha-MT. These results suggest that the suppressive effect of neuroleptics on the conditioned behavior is selectively potentiated by alpha-MT, and not influenced by PCPA. 16 references. (Author abstract)

002291 Ornstein, Kurt; Huston, Joseph P. Inst. Psych., Univ. Dusseldorf, Lab. Comp. and Phys. Psych., Universitatsstrasse 1, D-4000 Dusseldorf, Germany **Interaction between morphine and reinforcing lateral hypothalamic stimulation.** Psychopharmacology (Berlin). 54(3):227-235, 1977.

The interaction between morphine and lateral hypothalamic self-stimulation in rats was investigated in three experiments. In nonaddicted animals injections of moderate doses of morphine resulted in a short lasting increase in the self-stimulation threshold. Injections of low doses did not alter the self-stimulation threshold significantly. In addicted animals self-stimulation thresholds were significantly lower 2 h compared to 22 h after injection of morphine hydrochloride. A 16mg/kg injection of morphine in nonaddicted rats suppressed self-stimulation. However, when the animals were administered noncontingent priming stimulation and were hand shaped toward the lever whenever they left it, they continued to lever press throughout the entire 90 min postinjection testing period. The animals that were neither primed nor shaped (and therefore remained unstimulated), however, showed a significantly better recovery when tested 90 min after the injection; i.e. their response rate was higher than that of the primed and shaped animals, which were engaged in bar pressing throughout the entire testing procedure. 44 references. (Author abstract)

002292 Overton, Donald A. Eastern Pennsylvania Psychiatric Institute, Philadelphia, PA **Basic mechanisms of state-dependent learning.** Psychopharmacology Bulletin. 14(1):67-68, 1978.

A summary of an ongoing research project on basic mechanisms of state-dependent learning is presented. An attempt to neuroanatomically localize the brain mechanisms underlying state-dependent learning and the study of drug discrimination in rats are described as the goals of the project. In the drug discrimination procedure, Ss are trained to respond differentially to localized microinjection of various drugs. In this manner, 14 drugs are tested to determine the intracerebral dose of each drug that yields discriminative control.

002293 Parvizi, N.; Naftolin, F. Institut fur Tierzucht und Tierverhalten FAL, Mariensee, 3057, Neustadt 1, Germany **Effects of catechol estrogens on sexual differentiation in neonatal female rats.** Psychoneuroendocrinology (Oxford). 2(4):409-411, 1977.

To investigate the role of catechol estrogens in reproduction by assessing the effects of neonatal administration of 2-hydroxyestradiol-17beta and 2-hydroxyestrone on the timing of vaginal opening and sexual cyclicity and fertility a study was conducted. Results confirm the action of primary estrogens and indicate the effectiveness of catechol estrogens in causing defeminization. Since catechol estrogens are strong competitive inhibitors for methylation of catecholamines in the brain as well as in peripheral structures, they could be acting as estrogen agonists/antagonists or via changes in catecholamine metabolism. It is conceivable that estradiol acts in a similar manner at the hypothalamic levels after hydroxylation or other metabolism. 7 references.

002294 Pfister, William R.; Yim, George K. W. Department of Pharmacology and Toxicology, Purdue University, West Lafayette, IN 47907 **Formamidine induced feeding and behavioral alteration-in the rat.** Federation Proceedings. 36(3):352, 1977.

The effect of two formamidine pesticides, chlordimeform and amitraz, on feeding and other behavior in the rat will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Chlordimeform possessed many amphetamine-like actions: weak MAO inhibition, psychomotor stimulation, stereotypic behavior and, at a dose of 60mg/kg i.p.,decreased food intake and weight loss. However, at 10mg/kg, chlordimeform increased 3 hr food intake eightfold and 24 hr food intake increased 20%. A daily dose of 6mg/kg chlordimeform caused little weight change after 6 days. Chlordimeform induced hyperphagia was antagonized by amphetamine and fenfluramine, while propranolol, phenoxybenzamine, and haloperidol had little or no effect. Amitraz increased 3 hr food intake by a factor of 6.5. (Journal abstract modified)

002295 Poling, Alan; Urbain, Cathleen; Thompson, Travis. Psychiatry Research Unit, University of Minnesota, Box 392 Mayo Memorial Building, Minneapolis, MI 55455 **Effects of d-amphetamine and chlordiazepoxide on positive conditioned suppression.** Pharmacology Biochemistry and Behavior. 7(3):233-237, 1977.

The effects of acute administration of d-amphetamine and chlordiazepoxide under a positive conditioned suppression procedure paradigmatically similar to that studied by Miczek was studied in six rats under a number of parameters including baseline reinforcement schedule, deprivation level under which Ss were tested, length and frequency of presentation of the prefood stimulus, and (in some cases) drug doses given. The rats first leverpressed under a variable interval 80 sec food reinforcement schedule. After response had stabilized, an 8 sec tone terminating with food delivery was superimposed on the variable interval schedule on the average once every 5 minutes without regard to the animal's behavior. This positive conditioned suppression procedure consistently reduced responding during the prefood stimulus (tone). Neither d-amphetamine nor chlordiazepoxide significantly affected the relative suppression produced by the tone. Instead both drugs produced generally nonselective effects, similarly affecting response rate in the presence and absence of the tone. 24 references. (Author abstract modified)

002296 Poppei, M.; Hecht, K.; Hecht, T.; Treptow, K.; Moritz, V.; Choinowski, S. Central Inst. for Research of Heart

& Circulatory Regulations, Academy of Sciences of the GDR, DDR-1115 Berlin-Buch, Germany **Prevention of environmental stress impact on rats.** Activitas Nervosa Superior (Praha). 19(4):313-314, 1977.

A summary of a paper read at the 2nd International CIANS Congress on prevention of environmental stress impact on rats is presented. Experiments on albino rats over the course of 12 weeks revealed that the neurotogenic and hypertensive action of stress could be prevented by daily alternation of locomotor exercise and stress (in the form of intermittent immobilization). A similar preventive effect was obtained by administration of CH100, a test substance based on the diisopropylamine salt of p-chlorophenoxyacetic acid. The mechanisms underlying these effects are discussed.

002297 Rech, R. H.; Vomachka, M. K.; Rickert, D. E. Department of Pharmacology, Michigan State University, East Lansing, MI 48824 **Interactions between depressants (alcohol-type) and stimulants (amphetamine-type).** Pharmacology Biochemistry and Behavior. 8(2):143-151, 1978.

Alcohol type depressants and amphetamine type stimulants were administered to rats to determine the interactions between these classes of drugs, utilizing the rotarod performances of rats. The combination of 1.5g/kg of ethanol with 8mg/kg d-amphetamine induced prolonged coma and death. Combinations of 8mg/kg d-amphetamine with depressants other than alcohol did not cause coma and death; methaqualone and amphetamine, in fact, showed a trend toward antagonism. Variations in dosages of both drugs produced no predictable changes in the rate of elimination of either drug. It was demonstrated by the study that central stimulants of the amphetamine type and depressants of the barbituate ethanol class interact to influence rotarod performance of rats in ways not predictable on the basis of the separate effects of each agent. 25 references.

002298 Redmond, D. Eugene, Jr. Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510 **Alterations in the function of the nucleus locus coeruleus: a possible model for studies of anxiety.** In: Hanin, I., Animal models in psychiatry and neurology. Elmsford, N.Y., Pergamon Press, 1977. 499 p. (p. 293-304).

In a paper presented at a workshop on animal models in psychiatry and neurology held in Rockville, Maryland, in June 1977, studies in monkeys comparing the behavioral effects of various manipulations which increase or decrease locus coeruleus (LC) functioning to the behavioral effects produced by the presentation of threatening but nonpainful stimuli are discussed in terms of modification of LC functioning as a possible animal model for human anxiety. Electrical stimulation of the LC or dorsal noradrenergic bundle, administration of piperoxane, and presentation of a painful stimulus, all of which increase LC functioning, produce behavioral effects virtually indistinguishable from those produced by presentation of a fear stimulus or a frightening situation with no identifiable threat. Lesioning of the LC and administration of clonidine, morphine, diazepam, or propranolol, which decrease LC functioning, all decrease or eliminate the elicited behaviors. Some criteria for a central neurophysiological model of anxiety are presented and the results of the LC functioning studies are discussed in terms of whether they meet these criteria. It is suggested that the relevance of the studies in monkeys to human anxiety is supported by evidence that known antianxiety drugs decrease LC functioning and by the fact that piperoxane, which increases LC functioning, produces anxiety in humans. It is also suggested that the data support an alarm system function for the LC, and that human anxiety may be a part of this alarm system. 76 references.

002299 Roberts, D. C. S.; Fibiger, H. C. Division of Neurological Sciences, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia V6T 1W5, Canada **Lesions of the dorsal noradrenergic projection attenuate morphine- but not amphetamine-induced conditioned taste aversion.** Psychopharmacology (Berlin). 55(2):183-186, 1977.

To elucidate the role of the dorsal noradrenergic (NA) system in amphetamine and morphine induced conditioned taste aversions (CTA), the effects of 6-hydroxydopamine(6-OHDA) lesions along the dorsal segmental NA pathway were assessed in rats. Lesions resulted in the extensive depletion of NA in the hippocampus and cortex of test animals, and severely attenuate the CTA to saccharin normally produced by repeated pairings with 10mg/kg morphine. This is interpreted as a specific change in the punishing properties of morphine and not a deficit in the ability of 6-OHDA treated animals to learn a CTA, since identical lesions in other groups of rats failed to affect the CTA induced by 0.5or 1.0mg/kg d-amphetamine. 24 references. (Author abstract modified)

002300 Saelens, J. K.; Welch, J.; Robson, R. D.; Roffman, M. Research Department, Pharmaceuticals Division, Ciba-Geigy Corporation, Summit, NJ 07901 **Effect of baclofen (Bl) (Lioresal (R) on dopaminergic single units and Sidman avoidance behavior.** Federation Proceedings. 36(3):395, 1977.

The effect of baclofen on the firing rate of single neurons and on Sidman avoidance responding in rats was reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Baclofen i.v. depressed the firing rate of dopaminergic neurons in the zona compacta and ventral tegmentum in rats immobilized by gallamine and ventilated artificially. At 5mg/kg i.v. or i.p.,but not at 2.5mg/kg, baclofen reduced avoidance responding. Haloperidol increased the firing rate of most of these neurons, and 0.5to 2mg/kg baclofen i.v. antagonized this increase, reducing the firing rate below the control baseline. Baclofen, 2.5mg/kg i.p.,potentiated the avoidance blocking properties of haloperidol and chlorpromazine. The avoidance blocking properties of baclofen may be related to its ability to reduce the firing rate of dopaminergic neurons. (Journal abstract modified)

002301 Sanders, Barbara; Sharpless, Seth K.; Collins, Allan C.; McClearn, Gerald E.; Flanagan, Colleen. Institute for Behavioral Genetics, Univ. of Colorado, Boulder, CO **Activating and anesthetic effects of general depressants.** Psychopharmacology (Berlin). 56(2):185-189, 1978.

In a study of the activating and anesthetic effects of general depressants, the long sleep (LS) and short sleep (SS) lines of mice were derived by selective breeding with respect to ethanol sleep time. It was found that in current generations LS mice also have longer sleep times than SS mice to trichloroethanol and paraldehyde. Two subsequent experiments tested the hypothesis that mice that are relatively insensitive to the hypnotic effects of depressant drugs might be relatively activated by low doses of these drugs. Both experiments failed to support the hypothesis. First, although SS mice were more activated than LS mice by subhypnotic doses of paraldehyde, the lines did not differ in the degree of activation produced by low doses of trichloroethanol. Second, among mice from a genetically heterogeneous population (HS), there was no relation between the degree of activation induced by a low dose of ethanol and sensitivity to the hypnotic effects of a higher dose. 12 references. (Author abstract modified)

002302 Scott, John P. Bowling Green State University, Bowling Green, OH **Animal model for study of hyperkinesis and aggression.** Psychopharmacology Bulletin. 14(1):68, 1978.

A summary of an ongoing research project undertaken to develop a canine model for the study of hyperkinesis and aggression within social systems is described. Immediate goals of the project are to develop simple and realistic test situations that measure hyperactivity and aggression, to determine the optimum age for such tests, and to demonstrate that the paradoxical effect of amphetamine can be reliably elicited in dogs classified as hyperactive. Litters of beagles, telomians, and reciprocal F1 hybrids were tested for hyperactivity, aggression and paradoxical effect of amphetamine. Dogs not classified as hyperactive have also shown the paradoxical response (improved inhibition) to amphetamine, suggesting that hyperactivity and the paradoxical response may be mediated by independent genetic systems in this species.

002303 Sepinwall, Jerry; Grodsky, Fred S.; Cook, Leonard. Dept. of Pharmacology, Hoffmann-La Roche Inc., 340 Kingsland St., Nutley, NJ 07110 **Conflict behavior in the squirrel monkey: effects of chlordiazepoxide, diazepam and N-desmethyldiazepam.** Journal of Pharmacology and Experimental Therapeutics. 204(1):88-102, 1978.

A study was conducted to examine the effects of chlordiazepoxide, diazepam and N-desmethyldiazepam on conflict behavior in squirrel monkeys. Dose response profiles were determined for chlordiazepoxide, diazepam and N-desmethyldiazepam in a squirrel monkey punishment (conflict) procedure. The monkeys were trained to lever press under a food maintained concurrent schedule consisting of an unpunished 6 minute variable-interval (VI) schedule, and a 1.5minute VI schedule, on which responses were punished intermittently with electric footshocks. The three benzodiazepines effectively increased responding that had been suppressed by punishment; they had inverted U-shaped dose effect curves. The following observations were also made: 1) during initial training, as shock intensity was increased and punished responding became suppressed, some monkeys exhibited an increase in unpunished response rates which may have represented positive behavioral contrast, but response rate changes were associated with changes in the amount of time the monkeys allocated to each schedule; 2) at certain dose levels, all three compounds exerted antipunishment effects 24 hours after administration; and 3) when the monkeys had no previous drug experience they were more sensitive to the depressant effects of the benzodiazepines. With repeated administration, there was a reduction in this sedation and a concomitant increase in the antipunishment effect. This phenomenon was dose and animal dependent. 49 references. (Author abstract modified)

002304 Shah, S. N.; Bhargava, V. K.; Johnson, R. C.; McKean, C. M. Brain-Behavior Research Center, LPNI, Sonoma State Hospital, Eldridge, CA 95431 **Effect of p-chlorophenylalanine (PCPA) and phenylalanine (PHE) treatment on early auditory evoked responses in rats.** Federation Proceedings. 36(3):353, 1977.

The effect of p-chlorophenylalanine (PCPA) and phenylalanine on brain development, serotonin content, and auditory evoked response in the postnatal rat was reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Rats were given PCPA alone or in combination with phenylalanine twice daily from the 5th postnatal day until the 20th or 30th days, and a control group received saline. PCPA alone produced reductions in brain weight and myeline content, and PCPA plus phenylalanine produced a greater weight reductionplus Serotonin content was also decreased. At 20 or 30 days, early auditory evoked responses generated from acoustic relays between the cochlear and rostral brainstem were recorded from scalp electrodes. There were significant increases in latency in the brainstem potentials of all animals treated with PCPA alone and with PCPA plus phenylalanine. The drug combination produced greater increases in latency. The low myelin and serotonin content and the low brainweight correlated with the slow auditory evoked responses. (Journal abstract modified)

002305 Shea, P. A.; Hingtgen, J. N.; Aprison, M. H. Institute of Psychiatric Research, Indiana University of School of Medicine, Indianapolis, IN 46202 **Decreased response inhibition during fixed-interval responding in pigeons following atropine administration.** Federation Proceedings. 36(3):353, 1977.

Role of the cholinergic system in different types of response inhibition will be discussed at the 61st annual meeting of the Federation of American Societies for Exeperimental Biology, Chicago, 1977. Pigeons trained to work on a multiple fixed-ratio 50, fixed-interval 10 schedule of food reinforcement displayed lower rates of responding during the first 3 min of the 10 min fixed-interval component than during the last 7 min. To determine possible cholinergic involvement during the 3 min period of low responding, atropine was given i.m. to pigeons 20 min prior to testing of the above schedule. Response rates for the initial 3 min segment doubled when compared with control rates, whereas overall response rates decreased by almost half. Methylatropine caused no behavioral change. (Journal abstract modified)

002306 Shelburne, Samuel A., Jr.; McLaurin, Robert L. University of Cincinnati College of Medicine, Cincinnati, OH **The effects of phencyclidine on visually evoked potentials of rhesus monkeys.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(1):95-98, 1977.

Phencyclidine (Sernylan) was given intramuscularly to 12 rhesus monkeys and electroencephalograms and visually evoked potentials to photic stimulation were recorded. Phencyclidine has profound effects upon VEPs, particularly a marked enhancement of positive components maximal around 100msec after stimulus presentation. Most likely these effects are related to the level of surgical anesthesia, Stage III, phase I. A correlation was suggested between the increased amplitude of VEPs and the psychotic clinical manifestations of visual perceptual distortions. It is suggested physicians and investigators should be aware of the striking effects of this compound, now widely used as a street drug (angel dust), on neurophysiological functions. 12 references. (Journal abstract)

002307 Shibuya, Takeshi; Matsuda, Hiromi; Sato, Katsuhiko; Chen, Pochung; Hayashi, Masaaki; Fujita, Yutaka; Ukita, Tsuneo; Nishimori, Tsukao. Dept. of Pharmacology, Tokyo Medical College, Tokyo, Japan **Pharmacological study of amoxapine, a dibenzoxazepine derivative.** Journal of the Tokyo Medical College (Tokyo). 35(1):115-129, 1977.

Inhibitory effects of amoxapine, a derivative of dibenzoxazepine, on the spermatogenic and central nervous systems of monkeys, dogs, cats, and rats are reported. A cataleptogenic effect was further observed in monkeys; body temperature decreased in rats; and in dogs, anti-apomorphine activity was shown. Inhibition of conditioned avoidance response was demonstrated in rats, while spinal monosynaptic and polysynaptic reflexes were inhibited in cats. In large doses,

amoxapine decreased brain serotonin, dopamine, and noradrenaline and inhibited spermategenesis in rats. It is suggested that the action mechanism is different from imipramine. 23 references. (Author abstract modified)

002308 Sobrian, Sonya K. Pharmacology, School of Medicine, Howard University, Washington, DC 20059 **Prenatal morphine administration alters behavioral development in the rat.** Pharmacology Biochemistry and Behavior. 7(3):285-288, 1977.

Female rats were administered increasing doses of morphine sulfate 5 days prior to mating and during gestation until 4 to 6 days before the birth of their litters. Prenatal morphine exposure altered the normal developmental pattern of spontaneous motor activity by inducing in the offspring a sustained period of hyperactivity during the 3rd and 4th postnatal week. This disruption in behavioral ontogeny did not coincide with changes in physical parameters. Decreased body weight and higher mortality were observed in morphine treated offspring only during the first postnatal week. The appearance of behavioral disturbances in the absence of physical abnormalities emphasizes the need for followup studies of infants born to narcotic dependent mothers after signs of physical withdrawal or retarded growth have disappeared. 21 references. (Author abstract)

002309 Solomon, Paul R.; Kiney, Colleen A.; Scott, David R. Department of Psychology, Bronfman Science Center, Williams College, Williamstown, MA 01267 **Disruption of latent inhibition following systemic administration of p-chlorophenylalanine (PCPA).** Physiology & Behavior. 20(3):265-271, 1978.

Two experiments were undertaken in rats to examine disruption of latent inhibition effects following systemic administration of p-chlorophenylalanine (PCPA). Rats received either no or 30 preexposures to a tone which was later used as a conditioned stimulus in a two-way active avoidance task. Tone preexposure resulted in retarded conditioning in normal animals. This latent inhibition effect, however, was not present in rats treated with PCPA. A second experiment used the combined cue summation test to verify the fact that stimulus preexposure endowed the tone with latent and not conditioned inhibitory properties. The results were discussed in terms of the role of the serotonergic mesolimbic system in tuning out irrelevant stimuli. 47 references. (Author abstract modified)

002310 Sonderegger, Theo; Zimmermann, Emery. Department of Psychology, University of Nebraska, Lincoln, NE **Adult behavior and adrenocortical function following neonatal morphine treatment in rats.** Psychopharmacology (Berlin). 56(1):103-1109, 1978.

Adult behavioral and endocrine effects of neonatal administration of morphine (M) were studied in female rats injected subcutaneously with M on either days 3 to 12 (M1) or days 12 to 21 (M2). The dose given twice daily was increased to 8mg/kg in group M1 and to 16mg/kg in group M2. Compared to saline treated controls, growth rates were temporarily suppressed and bodyweights were reduced until day 20 in M1 and until day 64 in M2 rats. The open-field test performed on days 29 to 31 failed to differentiate between neonatal treatment groups. On days 90 to 95 M1 but not M2 animals showed impaired learning of a conditioned emotional responses (CER). On day 40 all groups showed similar increased levels of plasma corticosterone 30 min following injection of naloxone. Compared to controls on day 156, both M1 and M2 rats showed diminished analgesic responses to M. In response to M challenge on day 170, all groups showed comparable acute increases in plasma corticosterone levels. These findings provide further evidence that early exposure to M results in growth retardation and protracted tolerance and that, depending on dose and time of exposure, neonatal M may result in impaired learning of CER in adulthood. These effects suggest that early morphine can produce long-lasting alterations of learned behavior without lasting impairment of pituitary/ adrenal function. 30 references. (Author abstract)

002311 Sorenson, Charles A.; George, Stephen A.; Friedman, Andrew J. Neuroscience Program, Amherst College, Amherst, MA 01002 **The effect of D-amphetamine on gamma efferent activity in the acute decerebrate rat.** Brain Research (Amsterdam). 143(2):387-391, 1978.

To determine whether descending norepinephrine (NE) containing neurons might play a role in locomotion, electrophysiological changes following administration of D-amphetamine were monitored in the decerebrate rat (n=4). Amphetamine produced the same changes in static and dynamic gamma efferents as seen in the DOPA treated spinal cat or the decerebrated cat stimulated in the mesencephalic locomotor region (MLR). Results provide evidence that amphetamine induced behavioral stimulation in both the rat and the cat is due at least in part to activation of the MLR which exerts its influence through the release of NE at the segmental level. In view of these findings, caution should be exercised in assuming that it is the ascending pathways which mediate the behavioral effects of pharmacological agents acting on the catecholaminergic systems in intact animals. 18 references.

002312 Soubrie, P.; Simon, P. Unite de Neuropsychopharmacologie-U. 19, INSERM, 2 Rue d'Alesia, F-75014 Paris, France **Comparative study of the antagonism of bemegride and picrotoxin on behavioural depressant effects of diazepam in rats and mice.** Neuropharmacology (Oxford). 17(2):121-125, 1978.

A series of studies were carried out in rats and mice to examine the comparative effects of bemegride and picrotoxin on the behavioral depressant effects of diazepam. Results show the bemegride and diazepam act as antagonists. Bemegride counteracted diazepam induced hypokinesia and amnesic-like activity, diazepam-induced motor incoordination, and reduced grip strength. A gamma-aminobutyric acid (GABA) receptor blocking agent, picrotoxin also markedly antagonized all (except for hypokinesia) these diazepam effects. Diazepam exerted similar dose related antagonisms on bemegride and on picrotoxin induced seizures. Both antagonisms were observed at lower doses than were required for strychnine induced seizure inhibition. Picrotoxin/diazepam antagonism seems to further support the possibility of a GABAminergic mechanism of action of benzodiazepines depressant effects. Bemegride/diazepam antagonism is discussed in terms of a possible inhibitory role of bemegride on GABAminergic transmission. 14 references. (Author abstract modified)

002313 Spierings, E. L. H.; Dzoljic, M. R.; Godschalk, M. Erasmus University, Rotterdam, The Netherlands **Effect of clozapine on the sleep pattern in the rat.** Pharmacology (Basel). 15(6):551-556, 1977.

The effect of clozapine on the sleep pattern in the rat was studied after a single injection (2.5to 20mg/kg) and after daily administration for 11 consecutive days (2x20mg/kg/day). After a single injection clozapine significantly suppressed REM sleep in a dose related way, leaving slow wave sleep (SWS) unchanged. Following chronic administration, however, clozapine exerted its most prominent effect on SWS, the

enhancement of which persisted for at least 3 days after discontinuation of treatment. REM sleep decreased with the development of tolerance and in the absence of rebound phenomena. The results are discussed in the light of disturbances in brain monoamines and the tolerance these amines developed to repeated administration of clozapine. 20 references. (Author abstract)

002314 Steranka, L. R.; Sanders-Bush, Elaine; Barrett, R. J. Tennessee Neuropsychiatric Institute, Nashville, TN **Tolerance to p-chloroamphetamine's effects on Sidman avoidance performance and catecholamine metabolism.** Neuropharmacology (Oxford). 16(11):761-769, 1977.

Rats trained to bar press to avoid shock in a nondiscriminated, Sidman avoidance paradigm were injected intraperitoneally with either saline or 5mg/kg of p-chloroamphetamine (PCA) twice daily for 7.5days. When tested 48 hr later, the administration of PCA increased response rates in saline pretreated but not PCA pretreated rats, indicating the development of physiological tolerance. Complete recovery from tolerance was observed within 2 weeks after the termination of chronic drug treatment. The rates of disappearance of PCA from the brains of tolerant and nontolerant rats were similar, suggesting that tolerance was not due to an altered disposition of the drug. The effects of acute and chronic PCA administration on the conversion of (3H)-tyrosine to (3H)-norepinephrine and (3H)-dopamine and in vivo tyrosine hydroxylase activity were measured in whole brains 15 min after PCA administration. The acute administration of PCA increased the formation of both catecholamines and increased in vivo tyrosine hydroxylase activity. However, neither of these effects was observed in tolerant rats challenged with PCA. These data suggest that tolerance to the facilitatory effect of PCA is associated with tolerance to the ability of the drug to increase the rate of synthesis of catecholamines. 34 references. (Author abstract)

002315 Stolerman, I. P.; D'Mello, G. D. MRC Neuropharmacology Unit, Medical School, Birmingham B15 2TJ, England **Amphetamine-induced taste aversion demonstrated with operant behaviour.** Pharmacology Biochemistry and Behavior. 8(2):107-111, 1978.

To study the possible effects of flavor/amphetamine pairings on operant behavior, rats were trained to press bars for water reinfocers delivered after every 40 responses, and flavored reinforces were then substituted for the water and postsession injections of amphetamine (1mg/kg) were given. Even a single flavor/amphetamine pairing produced some decrement in responding for that flavor, whereas three flavor/amphetamine pairings almost completely suppressed responding. In the same rats, a flavor which was paired with saline injections did not suppress responding. It is concluded that flavor/amphetamine pairings can have a powerful influence on operant behavior and that the different outcomes of flavor conditioning and self-administration procedures cannot be attributed simply to the type of response required from the rat. 28 references. (Author abstract)

002316 Suomi, Stephen J.; Seaman, Stephen F.; Lewis, Jonathan K.; DeLizio, Roberta D.; McKinney, William T., Jr. Primate Laboratory, 22 North Charter Street, University of Wisconsin, Madison, WI 53706 **Effects of imipramine treatment of separation-induced social disorders in rhesus monkeys.** Archives of General Psychiatry. 35(3):321-325, 1978.

To examine the effects of imipramine on separation-induced social disorders in rhesus monkeys, two groups of young rhesus monkeys (n=8) were subjected to repetitive peer separations, a procedure that has been shown to produce depressive-like reactions in infant monkeys. Midway through the procedure one group was treated with the antidepressant, imipramine hydrochloride, the other with a saline placebo. In comparison with placebo treatment, the imipramine treatment yielded significant behavioral improvement in a form and with a time course similar to that seen when the drug is given clinically to human depressives. The implications of the findings are discussed. 27 references. (Author abstract modified)

002317 Szczawinska, Krystyna; Cenajek, Danuta; Chodera, Alfons; Wojciak, Zofia; Okulicz-Kozaryn, Irena. Zaklad Farmakologii i Farmakodynamiki AM, 10 Fredry, 61-701 Poznan, Poland **Pharmacodynamics and pharmacokinetics of psycholeptic drugs in the course of radiation disease: the effect of premedication with cystamine on pharmacodynamics and pharmacokinetics of nitrazepam.** Acta Physiologica Polonica (Warszawa). 28(2):161-168, 1977.

A study of the pharmacodynamics and pharmacokinetics of psycholeptic drugs in the course of radiation disease, particularly the effect of premedication with cystamine on the pharmacodynamics and pharmacokinetics of nitrazepam is presented. In the experiments carried out on rats radiation disease was evoked by exposure to 600 R. The strongest radioprotective action of cystamine was found on the third day of radiation disease. The tendency to normalization of both the pharmacodynamics (exploring mobility and anticonvulsant action) and pharmacokinetics of nitrazepam in the animals premedicated with cystamine was described. 21 references. (Journal abstract modified)

002318 Tabakoff, Boris; Ritzmann, Ronald F.; Yanai, Joseph. Department of Physiology, University of Illinois Medical Center, Chicago, IL 60612 **Tolerance to sedative hypnotics, memory and noradrenergic (NE) systems.** Federation Proceedings. 36(3):315, 1977.

The effect of 6-hydroxydopamine on development of tolerance to alcohol and other sedatives in mice will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Pretreatment of animals with 6-hydroxydopamine intraventricularly 7 days prior to chronic exposure to ethanol prevented development of tolerance to the hypnotic and hypothermic effects of ethanol, but did not prevent development of physical dependence. Desipramine given prior to the 6-hydroxydopamine prevented the disruption of tolerance by 6-hydroxydopamine. 6-Hydroxydopamine also prevented development of cross-tolerance to barbiturates, and combined treatment with desipramine and 6-hydroxydopamine restored the development of barbiturate cross-tolerance. 6-Hydroxydopamine disrupted CNS tolerance to pentobarbital induced by chronic treatment of mice with barbiturates. However, 6-hydroxydopamine did not interfere with ethanol tolerance when it was given after the tolerance was established. A similar function of noradrenergic systems was noted in memory consolidation processes. 1 reference. (Journal abstract modified)

002319 Tang, A. H.; Collins, R. J. Upjohn Company, Kalamazoo, MI 49001 **Enhanced analgesic effects of morphine after chronic administration of naloxone in the rat.** European Journal of Pharmacology (Amsterdam). 47(4):473-474, 1978.

The effect of chronic blockade of narcotic receptors induced by i.v. infusion of naloxone in the rat in which pain threshold and analgesic effect of morphine were determined by the tail

shock vocalization method on the day immediately before i.v. infusion and at weekly intervals is described. In a saline infusion group, morphine produced a significant elevation of the vocalization threshold each week, with the only exception on the fourth week after infusion. The same dose of morphine produced a much greater elevation in the vocalization threshold in the naloxone infusion group, beginning at the second week after infusion. After the experimental session on the fourth week of naloxone infusion, saline was substituted for naloxone for another 2 weeks of infusion. The difference between the two groups disappeared after these 2 weeks of saline infusion. 5 references.

002320 Terando, Loretta; Mirza, Noor; Zipnick, Jan; Overmier, Mary; Rossi, Nello; Reid, Larry D. Bradley University, Peoria, IL 61606 **Addictive agents and intracranial stimulation (ICS): daily morphine, self-stimulation, and parameters of ICS.** Physiological Psychology. 6(1):65-70, 1978.

Effects of daily doses of morphine across a range of intracranial stimulation (ICS) intensities were tested. Rats fixed with chronically indwelling bipolar electrodes pressed daily for direct electrical intracranial stimulation (ICS) of the hypothalamus. Rats pressed for a variety of intensities of ICS. As daily sessions with ICS continued, rats were given doses of morphine sulfate. The data confirm that morphine can accelerate pressing for ICS regardless of the intensities of ICS. One set of procedures indicated that programming ICS of about 75 microA (60 Hz sine waves of .25 sec) was sufficient to disrupt pressing previously sustained by intensities of 25 microA or lower. There were considerable individual differences in rats' reactivity to morphine; some showed marked acceleration of pressing while others showed little or no acceleration. These differences were not a direct function of intensity of ICS. 13 references. (Author abstract)

002321 Teuchmann, Jan Karol; Kania, Bogdan Feliks. Institute of Animal Physiology, Faculty of Veterinary Medecine, Agriculture Academy, Warsaw, Poland **The effects of etorphine, fentanyl and morphine on noradrenaline and dopamine concentrations in the striatum of rat.** Acta Physiologica Polonica (Warszawa). 28(2):107-112, 1977.

A study of the effects of etorphine, fentanyl and morphine on noradrenaline and dopamine concentrations in the striatum of rat is presented. Dopamine (DA) concentrations were determined after administration of etorphine (M 99 -- 0.008mg/kg), fentanyl (0.06mg/kg) and very high doses of morphine (20.0mg/kg). DA was chosen as a striatal neurotransmitter playing the main role in the extrapyramidal system. The concentrations of noradrenaline (NA) were determined for comparison. Etorphine in therapeutic doses and morphine in subtoxic doses increased the concentration of DA in striatal neurons. Since, under these conditions, the behavior of animals resumbles the symptom complex characteristic of the so-called parkinsonian or postneuroleptic syndrome in which a deficiency or absense of DA has been found in striatum, it might be supposed that the cataleptic action of etorphine and morphine may be due to inhibition of presynaptic striatal structures, with consequent disturbances in DA release from its stores. 19 references. (Journal abstract modified)

002322 Thomas, Karin V.; Handley, Sheila L. Pharmacological Laboratories, Department of Pharmacy, Aston University, Birmingham B4 7ET, England **Modulation of dexamphetamine-induced compulsive gnawing -- including the possible involvement of presynaptic alpha-adrenoreceptors.** Psychopharmacology (Berlin). 56(1):61-67, 1978.

In an investigation into the mechanism of amphetamine induced compulsive gnawing in the mouse, the effects of a range of drugs were determined on the lethality (ED50) value for dexamphetamine. Injection of noradrenaline or methoxamine into the cerebral ventricles (i.c.v.), or peripheral injection of clonidine, caused marked potentiation. The alpha-adrenoreceptor blocking agents phentolamine piperoxane and yohimbine elevated ED50 values while phenoxybenzamine was without significant effect. Inspection of effects on individual doses of dexamphetamine showed that both phenoxybenzamine and phentolamine could potentiate the effectiveness of low doses of dexamphetamine. Beta-adrenoreceptor blockade, using dl-propranolol or MJ-1999, significantly enhanced compulsive gnawing; d-propranolol was inactive. The selective dopamine blocking agent pimozide abolished compulsive gnawing, as did alpha-methyl-p-tyrosine. FLA63 also reduced compulsive gnawing. Cholinergic stimulation by carbachol and physostigmine i.c.v. or by arecoline antagonized dexamphetamine, while the muscarinic blocking agents atropine and hyoscine potentiated it. The 5-hydroxytryptamine (5-HT) depleting agent p-chlorophenylalanine potentiated the effect of low doses of dexamphetamine but had no net effect on ED50 values; reserpine behaved similarly. 5-HT itself abolished dexamphetamine gnawing. Clonidine caused marked potentiation of the gnawing induced by apomorphine. The results are discussed in terms of the possible involvement of several transmitter systems in modulating the compulsive gnawing syndrome. 46 references. (Author abstract)

002323 Todd, Janet Waring. University of Utah **Effects of posttraining injection of cholinergic agonists and antagonists into the amygdala on retention of passive avoidance training in rats. (Ph.D. dissertation).** Dissertation Abstracts International. Ann Arbor, MI, Univ. M-films, No. 77-20473 HC$15.00 MF$8.50 81 p.

The effects of posttraining injection of cholinergic agonists and antagonists into the amygdala on retention of passive-avoidance training were studied in 180 rats. Results suggested that injections of cholinergic agonists into the amygdala had profound effects on processes associated with retention. Injection of physostigmine (an anticholinesterase) or carbachol (a cholinomimetic) disrupted retention, whereas injection of atropine (an anticholinergic agent) did not disrupt retention. A low dose of atropine injected soon after physostigmine into the same amygdaloid loci counteracted the potential physostigmine induced retention deficit. It is concluded that pharmacological manipulation of activity in the amygdala via such posttraining injections may represent one approach to studying neurological processes associated with retention of aversive experiences in animals. (Journal abstract modified)

002324 van Ree, Jan M.; Slangen, Jef L.; de Wied, David. Rudolf Magnus Institute for Pharmacology, Medical Faculty, University of Utrecht, Vondellaan 6, Utrecht, The Netherlands **Intravenous self-administration of drugs in rats.** Journal of Pharmacology and Experimental Therapeutics. 204(3):547-557, 1978.

A standardized self-administration procedure in rats was used to determine the intravenous self-administration liability of graded doses of various drugs. Self-administration was reliably established with the tested addictive drugs (morphine, heroin, fentanyl and d-amphetamine), but not with the nonaddictive drugs (chlorpromazine and nalorphine). However, 1 out of 14 animals on nalorphine clearly demonstrated self-administering behavior. Self-administration was observed with delta1-tetrahydrocannabinol, but the percentage of animals

(40% on the highest dose) that initiated this behavior and the amount of drug intake were low in comparison with amphetamine and narcotics. Total daily drug intake was related to the unit dose delivered per injection in that a higher drug dosage led to more drug intake. In experiments with heroin, this relationship was not caused by prior forced injections. Narcotic drug administration resulted in a disturbance of the patterns of food and water intake. The present results indicate that measuring the reinforcing efficacy of drugs under strictly defined experimental conditions provides quantitative criteria for intravenous self-administration of drugs in rats. 35 references. (Author abstract modified)

002325 Viveiros, Donna M.; Tondat, Lynn Marie. Dept. of Psychology, SUNY at Brockport, Brockport, NY 14420 **Effects of sodium nitrite on DRL performance in the rat.** Pharmacology Biochemistry and Behavior. 8(2):125-127, 1978.

Fifteen Sprague-Dawley rats were administered sodium nitrite 0.10% or 0.15% solutions in their drinking water from the age of 45 days to determine the effect on response inhibition. At 80 days of age, rats were trained to bar-press for food pellets on a CRF schedule. After reaching criterion performance the rats were switched to a DRL-20 for a period of 6 days to test for response inhibition, which was measured as a ratio of responses to reinforcements. Results indicated no significant differences between groups for response inhibition. All groups showed significant increases in learning as reflected by a decrease in ratios and an increase in total reinforcements over days. However, sodium nitrite rats compared to controls obtained significantly fewer reinforcements over sessions and a greater number of no responding periods (time-outs). The possibility that sodium nitrite produced an increase in responding to distractible (nontask related) cues is discussed. 15 references. (Author abstract)

002326 Waddington, John L.; Longden, Adrian. Div. of Psychiatry, MRC Clinical Research Centre, GB-Harrow, Middlesex, HA1 3UJ, England **Rotational behaviour and cGMP responses following manipulation of nigral mechanisms with chlordiazepoxide: evidence for enhancement of GABA transmission by benzodiazepines.** Naunyn-Schmiedeberg's Archives of Pharmacology (Berlin). 300(3):233-237, 1977.

Rotational behavior and cyclic 3',5'-guanosine monophosphate (cGMP) responses following manipulation of nigral mechanisms with chlordiazepoxide were examined, and evidence is presented for enhancement of gamma-aminobutyric acid (GABA) transmission by benzodiazepines. Unilateral stereotaxic injections of 1 microgram of the soluble benzodiazepine chlordiazepoxide hydrochloride into the predominantly GABA containing zona reticulata of the substantia nigra of amphetamine pretreated rats induced rotational behavior similar to that seen following unilateral elevation of nigral GABA levels and amphetamine treatment; this effect was not seen following injections into the vicinity of the predominantly dopamine containing zona compacta. Chlordiazepoxide induced rotations were abolished by the GABA antagonist picrotoxin. Both chlordiazepoxide and GABA depresssed production of cGMP in samples of nigral tissue in vitro as estimated by radioimmunoassay. It is concluded that chlordiazepoxide may enhance GABA transmission within the substantia nigra, by some as yet unidentified mechanism, to create asymmetric activity in GABA modulated neurones and hence induce rotation. 34 references. (Author abstract modified)

002327 Walsh, Thomas J.; Palfai, Tibor. Syracuse University, Syracuse, NY 13210 **Time-dependent effects of reserpine on retention of passive avoidance.** Pharmacology Biochemistry and Behavior. 8(2):103-105, 1978.

Studies were conducted to investigate the generality of the amnesic gradient reported by Karpiak (1976) in passive avoidance. Reserpine was administered to mice before and after passive avoidance training. Reserpine produced amnesia for a one/trial passive avoidance task when given 2, 3, 4, 5 hr before but not when given 1, 8, 12, 24 hr or 30 min before, or immediately, 90 min or 2, 4, 5, 6, 8, 9, 12, 24 hr following training. The results are discussed in terms of the reserpine effect on biogenic amines and their role in memory formation. 20 references. (Author abstract modified)

002328 Warbritton, John D., III; Stewart, R. Malcolm; Baldessarini, Ross J. Mailman Laboratories for Psychiatric Research, McLean Division, Massachusetts General Hospital, Boston, MA **Decreased locomotor activity and attenuation of amphetamine hyperactivity with intraventricular infusion of serotonin in the rat.** Brain Research (Amsterdam). 143(2):373-382, 1978.

To evaluate the effects of continuously infused intraventricular serotonin (5-HT) on locomotor activity and on d-amphetamine induced hyperactivity, locomotor activity was monitored electronically and behaviorally in 5-HT treated rats and in normal controls. Sustained infusion of 5-HT has a sustained inhibitory effect on locomotor activity. This inhibition is continuous across the entire dose range from 0.6to 10.0microgram/microliter. Higher doses of 5-HT were severely toxic. In addition infusion of 5-HT decreased d-amphetamine induced hyperactivity and spontaneous locomotion by about two thirds at a dose of 5.0microgram/microliter. Results suggest that 5-HT is an effective inhibitor of locomotion both at high and at low levels of behavioral activation. In addition, there was no qualitative change in the type of behavior following intraventricular 5-HT given to either control or amphetamine pretreated rats. Findings provide further support for the concept that 5-HT functions normally as behaviorally inhibitory neurohumor in the mammalian CNS. 49 references.

002329 Weinberger, Susan Beth. Boston University Graduate School **A comparison of the effects of seizures and two anticonvulsant medications on learning in the Papio papio baboon. (Ph.D. dissertation).** Dissertation Abstracts International. Ann Arbor, MI, Univ. M-films, No. 77-21624 HC$15.00 MF$8.50 247 p.

The effects of anticonvulsant medications (diazepam and phenobarbital) and elicited seizures on repeated acquisition learning were studied in three prepubertal Papio papio baboons, a genetically epilepsy prone group. Middle dose therapeutic levels of both diazepam and phenobarbital improved learning performance relative to baseline controls. Since higher doses generally abolished performance gains, borderline behavioral toxicity may have occurred at the high dose levels. No seizure activity was observed prior to drug treatment in experimental Ss, and it is suggested that performance enhancement may be due to an underlying brain dysfunction rather than to elimination of the effects of seizures per se. Subsequent induction of seizures had no effect on performance except a small decrement 42 hr. after each seizure, suggesting that seizures may not be the cause of learning impairments in epileptics and that a limited number of seizures does not produce performance impairment. Of five additional animals who were unable to learn the repeated acquisition task, two were shown to have marked seizure responses, sug-

gesting that learning impairment may be related to susceptibility to epilepsy. It is concluded that diazepam and phenobarbital can improve learning performance and perhaps enable epileptics to express better their full performance potential. Further studies of learners and nonlearners suggest that underlying brain dysfunction, rather than the aftermath of seizures themselves, should be considered as a cause of learning difficulties found in many epileptics. (Journal abstract modified)

002330 Weiner, William J.; Goetz, Christopher; Nausieda, Paul A.; Klawans, Harold L. Department of Neurological Sciences, Rush-Presbyterian-St. Luke's Medical Center, 1753 West Congress Parkway, Chicago, IL 60612 **The effect of choline chloride on amphetamine- and apomorphine-induced stereotyped behavior.** Research Communications in Psychology, Psychiatry and Behavior. 3(1):55-63, 1978.

The effect of choline chloride on amphetamine and apomorphine induced stereotyped behavior in guinea-pigs was studied. Choline chloride, a precursor of central acetylcholine, inhibited the development of both forms of dopamine related stereotypy. The results indicate that choline chloride has a central behavioral effect and alters behaviors whose primary pathophysiology is related to dopamine. The central cholinergic effect of choline chloride is discussed in relation to the drug's reported clinical efficacy in human choreatic movements disorders. 10 references. (Author abstract)

002331 Wilson, Marvin C.; Buelke, Judy. Department of Pharmacology, School of Pharmacy, University of Mississippi, University, MS **Discriminative properties of l-amphetamine: stimulus generalization.** In: Ho, B., Drug Discrimination and State Dependent Learning. New York, Academic Press, 1978. 392 p. (p. 47-66).

Studies in rats of the efficacy of levoamphetamine as a discriminative stimulus at a dosage that minimally disrupts established operant performance and of stimulus generalization from this dose to other dosages of levoamphetamine and to other test compounds (methylphenidate, phenmetrazine, diethylpropion, chlorphentermine, fenfluramine, methoxamine and amantadine) are reported. Rats were trained on either a free operant avoidance schedule, a fixed-ratio 10 (FR-10) schedule of food reinforcement or a discriminated FR-10 schedule for food reinforcement using 1mg/kg of levoamphetamine or saline as the stimulus cues. The effects of the drugs were tested after stable operant performance was established and during extinction sessions of the discrimination procedure. Behavior observed following at least one dose of levoamphetamine, dextroamphetamine, phenmetrazine, diethylpropion, methoxamine and amantadine was similar to that elicted by 1mg/kg levoamphetamine. Behavior observed following fenfluramine, methylphenidate, and chlorphentermine was similar to saline baseline behavior or significantly different from both saline and levoamphetamine values. It is concluded that the interoceptive cue that establishes the levoamphetamine/saline discrimination is not based on anorexic activity or on increased activity as measured by enhanced avoidance responding. It is suggested that levoamphetamine discrimination may be based on central or peripheral dopaminergic or noradrenergic activation or a combination of these factors. 27 references.

002332 Wojciak, Zofia; Kozaryn, Irena; Chodera, Alfons; Szczawinska, Krystyna; Cenajek, Danuta. Zaklad Farmakologii i Farmakodynamiki Instytutu Biologiczno-Farmaceutycznego AM, Fredry 10, 61-701 Poznan, Poland **Changes in pharmacodynamics and pharmacokinetics of psycholeptic drugs in the course of radiation disease: effects of premedication with cystamine on dynamics and kinetics of thioridazine.** Acta Physiologica Polonica (Warszawa). 28(2):169-178, 1977.

A continuation of a previous study on pharmacodynamics and pharmacokinetics of psycholeptic drugs in the course of radiation disease is presented with emphasis on determination of the effect of premedication with cystamine on dynamics and kinetics of thioridazine. The effect of premedication with cystamine (100mg/kg) applied before irradiation on exploring mobility and cataleptic action of thioridazine was investigated in rats. The levels of thioridazine in blood serum, brain tissue and in bile were determined. It was found that cystamine prevents the changes in dynamics of thioridazine action in radiation disease through abolition of disturbances in kinetics of this drug. Half-life period of thioridazine was found to be reduced and its level in the brain tissue was diminished in the irradiated, cystamine pretreated animals in comparison with the irradiated, untreated ones. 18 references. (Journal abstract modified)

002333 Woods, James. Department of Pharmacology, University of Michigan, Ann Arbor, MI 48104 **Behavior effects of cocaine in animals.** In: Petersen, R., Cocaine: 1977. Rockville, MD NIDA, Research Monograph No. 13, 1977. 223 p. (p. 63-95).

Experimental work on the effects of cocaine on the behavior of animals is reviewed. The effects of cocaine on a variety of physiological systems are outlined, including pupil dilation, heartrate, and respiratory rate increases. Also discussed are the effects of cocaine on locomotor activity, aggression, and its use as a stimulus. It is concluded that the physiological effects of cocaine are produced by two prominent actions: the stabilization of membranes and the potentiation of the actions of the biogenic amines. Due to the paucity of information on human subjects, it is suggested that further studies of the behavioral action of cocaine in animals is especially important. 115 references.

002334 Wysocki, Charles J.; Nyby, John; Whitney, Glayde. Florida State University, Tallahassee, FL 32306 **Conditioned taste aversions: genotype by olfactory bulbectomy interaction.** Behavior Genetics. 8(1):119, 1978.

The disruptive effects of olfactory bulbectomy upon conditioned taste aversions are studied with attention to variability due to genetic factors. Using housemice, the ability of C57BL/6J, AKR/J and their reciprocal F1 hybrids to condition an aversion to saccharin was tested using lithium chloride. All genotypes were tested both with and without bilateral olfactory bulbectomies. Genotypic differences were observed in saccharin preference. These preferences were not affected by olfactory bulbectomy. As expected, all sham operated genotypes exhibited a marked saccharin aversion after lithium chloride conditioning regardless of normal preferences. While olfactory bulbectomy had little effect upon the ability of AKR's to condition an aversion, this operation severely disrupted C57 conditionability. The effects upon F1 conditionability were intermediate. The differential effects of bulbectomy on different genotypes may be due to sensory and/or nonsensory factors. (Journal abstract modified)

002335 Yaksh, Tony L.; Rudy, Thomas A. University College London, Department of Anatomy, Gower Street, London WC1 6BT, England **A dose ratio comparison of the interaction between morphine and cyclazocine with naloxone in rhesus monkeys on the shock titration task.** European Journal of Pharmacology (Amsterdam). 46(2):83-92, 1977.

Dose response curves were obtained for morphine and cyclazocine in rhesus monkeys performing the shock titration task, and the effects of naloxone on these curves were determined. Morphine and cyclazocine produced a dose dependent increase in the level of shock tolerated by the animal. Naloxone uniformly produced a dose dependent, parallel shift of the dose response curves to the right. However, naloxone had a lesser effect on the cyclazocine dose response curve than on the morphine dose response curve. The results are similar to those reported in prior experiments using rodents and other analgesiometric tests. The results are discussed in relation to the view that pure opiate agonists (morphine) and mixed agonists (cyclazocine) may differ in their receptor interaction with a given antagonist. The value of a behavioral procedure in which the ongoing drug response can be monitored, such as the shock titration task, in studies of this type is also discussed. 25 references.

002336 Yamamoto, I.; Ho, I. K.; Loh, H. H. Dept. of Hygienic Chemistry, School of Pharmacy, Hokuriku University, Kanagawamachi, Kanazawa 920-11, Japan **The antagonistic effects of 5-ethyl-5-(3-hydroxy-1-methylbutyl) barbituric acid on pentobarbital narcosis in both naive and tolerant mice.** Life Sciences (Oxford). 22(12):1103-1111, 1978.

Studies demonstrating that 5-ethyl-5-(3-hydroxy-1-methylbutyl)-barbituric acid (PB-OH), a major metabolite of pentobarbital, antagonizes pentobarbital induced narcosis in both naive and pentobarbital tolerant mice are reported. In PB-OH pretreated mice, the sleeping time induced by sodium pentobarbital was significantly shorter than that of the saline control animals. However, PB-OH failed to modify the pentobarbital induced hypothermia. The findings also demonstrated that hepatic microsomal enzyme activity and half-lives of pentobarbital and PB-OH in both plasma and brain were not modified by the pretreatment of PB-OH. The specific antagonistic effect of PB-OH appears to be a direct effect on sites in the CNS. 20 references. (Author abstract)

05 TOXICOLOGY AND SIDE EFFECTS

002337 Alexander, G. J. Neurotoxicology Research Unit, New York State Department Of Mental Hygiene, Bronx, NY 10461 **Lethality of pentylenetetrazol in rats after depletion of brain norepinephrine.** Federation Proceedings. 36(3):354, 1977.

Lethality of pentylenetetrazol as a function of brain norepinephrine and serotonin will be discussed at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. In Wistar-NTRU rats, the CD-50 for pentylenetetrazol was 50mg/kg and the LD-50 was 120mg/kg. Pretreatment with 300mg/kg p-chlorophenylalanine, which selectively decreased brain serotonin, lowered the pentylenetetrazol convulsive thershold and increased the percentage of seizures, but did not affect seizure severity. Pretreatment with 200mg/kg alpha-methyltyrosine, which decreased brain norepinephrine, did not alter the number of pentylenetetrazol induced seizures but increased their severity and lethality. Reserpine, which depleted both brain norepinephrine and serotonin, lowered the pentylenetetrazol seizure threshold and increased the incidence and the severity or lethality of seizures. Seizure incidence and frequency was related more to brain norepinephrine levels. Ability to mobilize catecholamines was critical to survival during seizures. (Journal abstract modified)

002338 Angrist, Burton; Rotrosen, John; Kleinberg, David; Merriam, Victor; Gershon, Samuel. New York University Medical Center, Department of Psychiatry, 550 First Avenue, New York, NY 10016 **Dopaminergic agonist properties of ephedrine -- theoretical implications.** Psychopharmacology (Berlin). 55(2):115-120, 1977.

In view of reported ephedrine induced psychoses resembling amphetamine psychosis, possible dopaminergic agonist properties of ephedrine were investigated in a series of stereotypy and neuroendocrine (prolactin suppression) studies in rats and in man. It was found that ephedrine produces dose related stereotypic behavior in rats which is antagonized by haloperidol but not by alpha-adrenergic or beta-adrenergic blockers. Pretreatment with alpha-methyl-p-tyrosine (AMPT), but not with reserpine, attenuated ephedrine induced stereotypy under one of two sets of conditions. Consistent prolactin suppression in human subjects was not seen. Findings are discussed in the context of clinical and pharmacological data regarding other dopamine agonist drugs. Data suggest that synergistic noradrenergic and dopaminergic facilitation may be important in the induction of stimulant psychoses. 30 references. (Author abstract modified)

002339 Bobritskaya, Z. M.; Gorbatko, L. G.; Litvinova, N. M.; Stolyarov, G. V. Khar'kovskiy nauchno-issledovatel'skiy institut nevrologii i psikhiatrii, Khar'kov, USSR /**Influence of extrapyramidal disturbances due to haloperidol on phenamine stereotypy and the effects of schizophrenic blood serum (experimental studies).**/ Vliyaniye ekstrapiramidnykh narusheniy, vyzvannykh galoperidolom, na fenaminovye steriotipii i effekti syvorotki krovi bol'nykh shizofreniyey (eksperimental'noye issledovaniye). Zhurnal Nevropatologii i Psikhiatrii imeni S. S. Korsakova (Moskva). 77(4):591-595, 1977.

Experiments performed with 78 white mice demonstrated that the appearance of extrapyramidal disorders depends on the schedule of haloperidol administration. Long-term administration of the drug leads to habituation, while termination leads to symptoms similar to withdrawal. The development of extrapyramidal disturbances does not increase antagonism of haloperidol in relation to phenamine, but does increase and prolong the activating action of blood serum of schizophrenic patients on the behavior of %77(4):597-601, 1977.

002340 Dobrin, E. I.; Berg, J. R.; Mares, S. E. Searle Laboratories Division, G. D. Searle & Company, Chicago, IL 60680 **Screening for the effects of dopaminergic and anti-dopaminergic drugs on serum prolactin levels by radioimmunoassay (RIA).** Federation Proceedings. 36(3):395, 1977.

Effects of neuropharmacologically active drugs on serum prolactin in rats were reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Study was undertaken because mammary tumors in animals treated with certain new neuroleptics and antiadrenergic drugs may be due to elevation of the prolactin level by the antidopamine properties of these drugs. Radioimmunoassay showed that dopamine may release prolactin inhibiting factor, which limits prolactin levels and prevents chronic stimulation of mammary tissue by prolactin. Dopaminergic compounds such as L-dopa, apomorphine, and amantadine decreased serum prolactin to minimal levels, while the antidopaminergic compounds alpha-methyldopa, reserpine, and other neuroleptics, caused elevations in serum prolactin. Morphine and prostaglandin A2 also caused an elevation in serum prolactin. The decreased serum prolactin induced by L-dopa was reversed by alpha-methyldopa and prostaglandin A2. (Journal abstract modified)

002341 Epstein, Paul N.; Altshuler, Harold L. Texas Research Institute of Mental Science, Texas Medical Center, Houston, TX 77030 **Increased haloperidol induced catalepsy after chronic cocaine treatment.** Federation Proceedings. 36(3):377, 1977.

Paper presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977, discusses haloperidol induced catalepsy and its antagonism by cocaine in rats pretreated with cocaine or saline. Male Sprague-Dawley rats were given cocaine or saline i.p. daily for 9 days. On the 10th day, haloperidol was given s.c. followed 80 min later by cocaine or saline solution i.p. Catalepsy, measured by the length of time a rat remained standing with forepaws over a 10cm high bar, was assessed at 20, 40, and 60 min after the haloperidol injection and 15 and 35 min after the cocaine injection. Catalepsy consistently lasted longer in the rats pretreated with cocaine. Cocaine injections 80 min after haloperidol were generally ineffective in antagonizing the catalepsy, regardless of pretreatment. Chronic cocaine appears to induce changes in dopaminergic systems. (Journal abstract modified)

002342 Gorodischer, R.; Warszawski, D.; Gordon, C.; Kaplanski, J. Soroka University Hospital, Beersheba, Israel **Comparative toxicity of caffeine and aminophylline in young and adult rats.** Israel Journal of Medical Sciences (Jerusalem). 13(11):1145-1146, 1977.

Results of a comparative study of caffeine and aminophylline toxicity in young and adult rats, presented at the 39th meeting of the Israel Physiological and Pharmacological Society in June 1977, are summarized. After administration of high doses of caffeine or aminophylline, adult rats developed lethargy, tonic convulsions and licking of lips. All deaths occurred within the first 24 hr. The LD50 for caffeine was 265mg/kg, and for aminophylline 207mg/kg. In one day old rats, the LD50 of caffeine was 230mg/kg at 24 hr and 157mg/kg at seven days. Administration of high doses of caffeine to newborn rats was associated with failure to gain weight. The group of newborn rats which received 100mg/kg had a 68% weight gain during the six days following the injection, whereas the groups of newborn rats who received 150mg/kg (and remained alive) had a 31% weight loss within five days following the injection. The LD50 of aminophylline in newborn rats was 178mg/kg at 24 hr. These results show that aminophylline is more toxic than caffeine both in adult and one day old rats and the toxicity of caffeine and aminophylline in the newborn rats, as opposed to the adult rats, is greater if observations are carried out for longer than one day. This may be due to the very long halflife of both methylxanthines in the neonate or to specific metabolic or behavioral changes (maternal rejection, poor feeding and so on). (Author abstract modified)

002343 Groom, G. V.; Evans, G. Tenovus Institute for Cancer Research, Cardiff, Wales **The effect of long-term administration of toxic doses of clomipramine on plasma prolactin, luteinizing hormone, follicle stimulating hormone and testosterone in the male rat.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):190-197, 1977.

To clarify the endocrine response to prolonged clomipramine therapy an investigation was conducted by administering toxic doses to male rats. The effects observed, notably on testosterone production, are discussed in terms of the mechanisms of action that may be involved and the possible clinical implications. All the animals treated long-term with clomipramine showed severe signs of distress and the mortality rate was high after administration of toxic doses. It is reported that the marked depression of both luteinizing hormone and follicle stimulating hormone levels in the plasma of the rats treated long-term with toxic doses of clomipramine is the first report of any effect of this drug directly on gonadotrophin secretion. 26 references.

002344 Hawkins, Richard; Kripke, Daniel F.; Janowsky, David S. Group in Physiology and Pharmacology, University of California, San Diego, CA **Circadian rhythm of lithium toxicity in mice.** Psychopharmacology (Berlin). 56(1):113-114, 1978.

To determine the existence of cyclical (circadian) variations in lithium toxicity in mice, mice, standardized to a light/dark cycle, were injected with lithium chloride (940mg/kg) at one of six times (20:00, 24:00, 4:00, 8:00, 12:00, and 16:00) and subsequently observed for mortality over 28 hr. A significant time of day effect was found for lithium induced lethality, with highest lethality following injection at 12:00. 8 references. (Author abstract)

002345 Hitri, Ana; Weiner, William J.; Borison, Richard L.; Diamond, Bruce I.; Nausieda, Paul A.; Klawans, Harold L. Department of Neurological Sciences, Rush-Presbyterian-St. Luke's Medical Center, 1725 West Harrison Street, Chicago, IL 60612 **Dopamine binding following prolonged haloperidol pretreatment.** Annals of Neurology. 3(2):134-140, 1978.

The number of binding sites for tritiated dopamine as well as the affinity of (3H)dopamine for dopamine receptors was studied in rats chronically pretreated with the neuroleptic haloperidol. The rats were given haloperidol for 14 or 21 days and were killed on day 21. It was found that 14 days of haloperidol pretreatment followed by drug withdrawal resulted in a 67% increase in the number of (3H)dopamine binding sites in the striatum and a ninefold increase in the affinity constant in the striatum. The same pretreatment regimen had no effect on either the number of receptor sites or the affinity constant in the nucleus accumbens. These results are consistent with the hypothesis that chronic neuroleptic pretreatment results in receptor site hypersensitivity in the striatum, which may be a major factor in the production of tardive dyskinesia. 35 references. (Author abstract)

002346 Johnels, Bo; Steg, Goran; Ungerstedt, Urban. Dept. of Neurology, Univ. of Goteborg, S-41345 Goteborg, Sweden **A method for mechanographical recording of muscle tone in the rat: the effect of some antiparkinsonian drugs on rigidity induced by reserpine.** Brain Research (Amsterdam). 140(1):177-181, 1978.

A method for mechanographical recording of muscle tone in the awake and intact rat is described, and results of a study using the method to examine the effects of some antiparkinsonian drugs on reserpine induced rigidity are summarized. The method makes use of repetitive measurements of the resistance to passive stretch of a muscle group, and may separate the differential effects of rigidity and spontaneous activity. Findings of the effects of apomorphine, levodopa, and bromocriptine on reserpine induced rigidity are discussed. It is concluded that the mechanographic method may contribute to the further analysis of animal models of extrapyramidal disease such as rigidity, hyperkinesia and akinesia. 6 references.

002347 Karler, Ralph. University of Utah, Salt Lake City, UT 84112 **/Toxicological and pharmacological effects of marihuana./** Toxicological and pharmacological effects. In: Petersen, R. C., Marihuana Research Findings: 1976. Rockville, MD, NIDA, Research Monograph No. 14, 1977. 251 p. (p. 67-85).

A toxicological and pharmacological assessment of marihuana which considers the known adverse effects of tobacco smoke on the lungs and the cardiovascular system is given. It is suggested from the results of animal studies that experimentally discernable effects on the lungs are produced by chronic exposure to marihuana smoke. Human experience with chronic exposure to tobacco smoke suggests that similar toxic effects will occur in response to marihuana smoke. It is concluded that marihuana or its principal psychoactive constituent, delta9-tetrahydrocannabinol, produces a variety of reversible effects but does not cause any irreversible pathological changes. These observations do not preclude the possibility that marihuana may produce some irreversible functional changes in humans, although no such evidence has yet been presented. 92 references.

002348 Kozaryn, Irena; Wojciakowa, Zofia; Chodera, Alfons; Szczawinska, Krystyna; Cenajek, Danuta. Zaklad Farmakologii i Farmakodynamiki Instytutu Biologiczno-Farmaceutycznego, Akademia Medyczna, 10 Fredry, Poznan 61-701, Poland **Pharmacodynamics and pharmacokinetics of psycholeptic drugs in the course of radiation disease: effect of premedication with metanabol on dynamics and kinetics of thioridazine.** Acta Physiologica Polonica (Warszawa). 28(3):263-270, 1977.

The effect of metanabol (1mg per kg) applicated to rats during 10 days before irradiation on pharmacodynamics and some indices of thioridazine kinetics was investigated. It was found that the increased cataleptic action of thioridazine (20mg per kg), during radiation disease was inhibited after metanabol premedication. The protective effect of metanabol was found to be due to shortening of the half-life time of thioridazine (from 5.5h in irradiated to 2.38 h in irradiated premedicated animals) as well as to lowering of thioridazine content in the brain tissue. 20 references. (Journal abstract)

002349 Lasky, D. I., Zagon, I. S., McLaughlin, P. J. Department of Psychology, Lebanon Valley College, Annville, PA 17003 **Effect of maternally administered heroin on the motor activity of rat offspring.** Pharmacology Biochemistry and Behavior. 7(3):281-284, 1977.

The behavior of 21-day-old rats whose mothers were administered heroin (5 mg/kg daily) throughout gestation and lactation was studied utilizing an activity wheel, activity cage, open field test, and step down latency times from an elevated platform. The total score of all behavioral tasks of offspring from heroin injected females was statistically different from that of pups from saline injected mothers, with heroin treated animals appearing more active. Findings suggest that drug abuse of heroin during pregnancy may have important implications in terms of the behavioral development of drug exposed children. 14 references. (Author abstract modified)

002350 Marcais, H.; Protais, P.; Costentin, J.; Schwartz, J. C. Lab. de Pharmacodynamie et de Physiologie, U.E.R. de Medecine et de Pharmacie, 49 Rue Maulevrier, F-76000 Rouen, France **A gradual score to evaluate the climbing behaviour elicited by apomorphine in mice.** Psychopharmacology (Berlin). 56(2):233-234, 1978.

A gradual score to evaluate the climbing behavior elicited by apomorphine in mice is described. A quantal evaluation of climbing behavior, taking frequency and duration into account, led to a biphasic dose response curve that reveals opposite actions of the dopamine agonist. Results suggest that climbing behavior, as presently evaluated, should represent a convenient single test to evaluate responsiveness of dopamine autoreceptors as well as postsynaptic dopamine receptors in striatum mediating the typical stereotyped climbing. 6 references. (Author abstract modified)

002351 no author. no address **Does diazepam maintain alcoholism?** World Medicine (London). 13(6):93, 1977.

Four groups of eight rats were studied to determine the relationship of diazepam treatment to maintained alcoholism. Ss, preconditioned or not preconditioned, were tested over 10 sessions for flavor preference by means of intragastric fistulation. During the last four sessions, the rats that had been preconditioned with alcohol, but had not been treated with diazepam, did not elect to be administered with alcohol any more often than the nonconditioned rats, but the preconditioned rats that had also been given diazepam before each test session continued to self-administer significantly more alcohol than any of the other three groups of rats. Results are interpreted as indicating that diazepam maintains the alcohol dependence that had been established by forced intubation.

002352 Pinto, J.; Wolinsky, M.; Rivlin, R. S. Department of Medicine, Columbia University, New York, NY 10032 **Inhibition of flavin synthesis by chlorpromazine in euthyroid and hyperthyroid rats.** Federation Proceedings. 36(3):369, 1977.

Inhibition of riboflavin conversion into flavin adenine dinucleotide (FAD) in the rat in vivo by chlorpromazine will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Adult male Holtzman rats were given thyroxine or saline i.p. for 8 days before sacrifice. Some rats also received chlorpromazine i.p. b.i.d. for 3 days before sacrifice. At 1 hr before sarifice, rats were given tritiated riboflavin s.c. Chlorpromazine inhibited the formation of tritiated FAD in both the saline treated and the thyroxine treated rat liver and heart. Kinetic studies showed that chlorpromazine competitively inhibited flavokinase, which converts riboflavin to flavin mononucleotide. 1 reference. (Journal abstract modified)

002353 Revazova, Yu. A.; Sidorov, V. P.; Radchenko, L. U. Nauchno-issledovatel'skiy institut po biologicheskim ispytaniyam khimicheskikh soedineniy, Moskovskaya oblast', Moscow, USSR **/The study of the mutagenic activity of luminal and pyrazidal./** Izucheniye mutagennoy aktivnosti lyuminala i pirazidola. Zhurnal Nevropatologii i Psikhiatrii imeni S. S. Korsakova (Moskva). 77(2):266-269, 1977.

The mutagenic activity of two psychotropic preparations, luminal and pyrazidol, was investigated in mice. It was demonstrated that luminal is capable of inducing chromosomal aberrations in bone marrow cells of mice, as well as dominant lethal mutations in post meiotic stages of spermatogenesis. Pyrazidol showed no mutagenic activity in the test studies. It is suggested these data be taken into account when treating individuals in the reproductive period of life. 8 references. (Journal abstract modified)

002354 Salazar, Margarita; Sokoloski, T. D.; Patil, P. N. College of Pharmacy, Ohio State University, Columbus, OH 43210 **Quantitation of binding of 3H-chlorpromazine to synthetic melanins and melanin granules.** Federation Proceedings. 36(3):383, 1977.

Affinity and capacity parameters for binding of chlorpromazine to synthetic melanins and melanin granules from bovine iris were discussed at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. The affinity of chlorpromazine for melanins synthesized from L-dopa, dopamine, L-alpha-methyldopa, and

D-alpha-methyldopa ranged from 218 to 590 million/M(-1), and the capacity ranged from 0.12 to 0.33nM/mg. Fluphenazine, haloperidol, and clozapine competed with chlorpromazine for binding to synthetic melanin from L-dopa. These three drugs competed equally with chlorpromazine when present in a ratio of 10:1. Chlorpromazine had about the same affinity for the melanin granules as for synthetic melanin, but the capacity of the granules was less than the capacity of the synthetic melanin. (Journal abstract modified)

002355 Schwarcz, R.; Scholz, D.; Coyle, J. T. Dept. of Pharmacology, Johns Hopkins University School of Medicine, Baltimore, MD 21205 **Structure-activity relations for the neurotoxicity of kainic acid derivatives and glutamate analogues.** Neuropharmacology (Oxford). 17(2):145-151, 1978.

The neurotoxic potency of glutamate analogs and derivatives of kainic acid was examined in the chick neural retina and the rat corpus striatum by measuring the effects of the agents on the activity of neurotransmitter synthesizing enzymes. In the retina, the order order of neurotoxic potency is kainate, ibotenate, quisqualate, N-methyl-D,L-aspartate, D,L-homocysteate, L-glutamate; whereas in the corpus striatum, the order of potency is kainate, ibotenate, N-methyl-D,L-aspartate, D,L-homocysteate, L-glutamate. In both the retina and corpus striatum, dihydrokainate, N-acetylkainate and kainic acid dimethylester are at least 45 to 100 times less toxic than kainate. These studies demonstrate a correlation between the neurotoxic and neuroexcitatory effects of glutamate analogs. 26 references. (Author abstract)

002356 Sklar, Lawrence S.; Amit, Zalman. Dept. of Psychology, Concordia Univ., Montreal, P.Q. H3G 1M8, Canada **Tolerance to high doses of morphine: lack of evidence of learning.** Behavioral Biology. 22(4):509-514, 1978.

Based on the hypothesis that tolerance to the analgesic effects of low doses of morphine may be mediated by learning, a study examined the generality of this hypothesis to both higher doses of morphine and to morphine effects other than analgesia. In the first experiment the LD50 dose of morphine was determined. The second experiment then examined the role of learning in the tolerance developed to a lethal dose of morphine by determining whether any possible learned associations between environmental stimuli and morphine injections could be extinguished. It was concluded that learning does not mediate the tolerance which can be developed to a lethal dose of morphine. 12 references. (Author abstract)

002357 Stefanini, E.; Longoni, R.; Fadda, F.; Spano, P. F.; Gessa, G. L. Institute of Pharmacology, University of Cagliari, Cagliari, Italy **Inhibition by lithium of dopamine-sensitive adenylate-cyclase in the rat brain.** Journal of Neurochemistry (Oxford). 30(1):257-258, 1978.

A study is presented in which the inhibition of dopamine sensitive adenylate cyclase from rat caudate nucleus is reported. Lithium concentrations that are inhibitory for this enzyme are above those concentrations attainable in brain after nontoxic doses of the alkali. Therefore, unless the adenylate cyclase in manic patients is more sensitive to lithium inhibition than the rat cyclase, the described inhibition may have more relevance for some central symptoms of lithium intoxication, such as tremors than for its antimanic action. The fact that concentrations of lithium sufficient to inhibit the stimulant response to dopamine did not lower enzyme activity suggests that the inhibition of lithium on dopamine sensitive adenylate cyclase is quite specific. 23 references.

002358 Szczawinska, Krystyna; Cenajek, Danuta; Chodera, Alfons; Wojciakowa, Zofia; Okulicz-Kozaryn, Irena. Zaklad Farmakologii i Farmakodynamiki, Instytutu Biologiczno-Farmaceutycznego, Akademia Medyczna, 10 Fredry, Poznan 61-701, Poland **Pharmacodynamics and pharmacokinetics of psycholeptic drugs in the course of radiation disease: effect of premedication with metanabol on dynamics and kinetics of nitrazepam.** Acta Physiologica Polonica (Warszawa). 28(3):255-261, 1977.

The effect of metanabol given to rats before irradiation on exploring motility and cataleptic action of nitrazepam was investigated. The level of nitrazepam in the blood plasma and urine was determined. Most evident radioprotective effect of metanabol was found on the third day after irradiation. The drug inhibited the increased response of the rats to the anticonvulsive action of nitrazepam and prevented the pharmacokinetic disturbances appearing in the course of radiation disease. 19 references. (Journal abstract)

06 METHODS DEVELOPMENT

002359 Antelman, Seymour M.; Caggiula, Anthony R. Dept. of Psychology, Western Psychiatric Inst. & Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261 **Tails of stress-related behavior: a neuropharmacological model.** In: Hanin, I., Animal models in psychiatry and neurology. Elmsford, N.Y., Pergamon Press, 1977. 499 p. (p. 227-245).

In a paper presented at a workshop on animal models in psychiatry and neurology held in Rockville, Maryland, in June 1977, the use of tail pinch induced behaviors (TPB) in rats as a model for human emotional stress related behaviors is discussed. The pressures used in the stimulus bound behavior which is dependent on the goal objects available. Studies using various norepinephrine (NE) antagonists and dopamine (DA) receptor blocking drugs, catecholamine (CA) synthesis inhibitors, and selective lesions to determine the brain site and the involvement of CA in the induction of TPB are reviewed. The studies suggest that the nigrostriatal DA system is involved in TPB. Studies of the effects of TPB of manipulations that influence brain serotonin (5-HT) activity are also reviewed. These manipulations include: 1) administration of 5-HT precursor loads; 2) administration of monoamine oxidase inhibitors to prevent 5-HT degradation; and 3) inhibition of 5-HT reuptake. These studies indicate that 5-HT may also be involved in TPB. The relevance of the TPB model for studying emotional stress induced behavior in humans is discussed. It is pointed out that: 1) humans under emotional stress show characteristics that are prominent features of TPB; 2) in both humans and animals, the performance of stimulus bound behaviors diminishes or prevents responses to unpleasant or painful stimuli; and 3) emotional stress induced overeating in humans and TPB eating in animals show similar responses to anorectic drugs. 97 references.

002360 Boisse, Norman R.; Okamoto, Michiko. Department of Medicinal Chemistry and Pharmacology, College of Pharmacy, Northeastern University, Boston, MA 02115 **Physical dependence to barbital compared to pentobarbital. I. "Chronically equivalent" dosing method.** Journal of Pharmacology and Experimental Therapeutics. 204(3):497-506, 1978.

To compare the physical dependence capability of a long (barbital) and short (pentobarbital) acting barbiturate in cats, the chronically equivalent dosing method was developed. Dose adjustment was sought for the directly observable central nervous system depressant effects which could be quantitated for

intensity by rating functional losses in neurologic response testing. Criteria for chronically equivalent dosing regimens were to provide equipotent doses of barbital and pentobarbital at intervals allowing equieffective recovery to correct for differences in potency, time/action, and degree of tolerance throughout chronic treatment. The maximally tolerable pentobarbital dosing method was used as the standard. From dose/response and time/action comparisons, a barbital dosing regimen was designed which provided equipotent doses (log potency ratio=1.04) at intervals (72 hours) allowing recovery equieffective to pentobarbital. The assumption of chronically equivalent central nervous system was confirmed for three quantitative response parameters: 1) peak central nervous system depression; 2) residual depression between doses; and 3) total depression based on areas under time/action curves. 23 references. (Author abstract modified)

002361 Calil, Helena M. Bldg. 10-Rm 4S-239, NIH, Bethesda, MD 20014 **Screening hallucinogenic drugs. II. Systematic study of two behavioral tests.** Psychopharmacology (Berlin). 56(1):87-92, 1978.

To evaluate two behavioral screening tests for hallucinogenic drugs, performance of rats following administration of a wide variety of hallucinogenic and nonhallucinogenic drugs was assessed for: 1) a discriminated Sidman avoidance test using modified Bovet-Gatti profiles which have been proposed as specific in detecting hallucinogenic activity; and 2) a state dependent learning drug discrimination test. By the first method, the hallucinogenic profile was obtained with both hallucinogenic and nonhallucinogenic drugs and, at least as used here, was not a suitable screening method. In the drug discrimination experiment, data from the present study along with other available evidence suggest the potential value of this method for drug screening procedures. 34 references. (Author abstract modified)

002362 Dafny, N.; Rigor, B. M. Department of Neurobiology and Anatomy, University of Texas Medical School, Houston, TX 77025 **Neurophysiological approach as a tool to study effects of drugs on the central nervous system: dose-effect of ketamine.** Experimental Neurology. 59(2):275-285, 1978.

To further examine a neurophysiological methodology for the study of drug central nervous system effects, effects of different doses of ketamine were studied in the inferior colliculus, the mesencephalic reticular formation, the ventromedial hypothalamus, and the somatosensory cortex of freely behaving rats. After recovery from surgery (6 to 8 days), the averaged acoustic field potentials following 32 repetitive stimuli were averaged to one trace. Four traces were recorded at 10 min intervals before and after ejection. Ten doses of ketamine were studied. The dose which induced surgical anesthesia was found to be 80mg/kg. Differences in the number of cases in which ketamine induced changes in sensory field potentials were observed between structures. The evoked responses in the somatosensory cortex exhibited dose dependent changes. The reticular formation and ventromedial hypothalamus were affected differently by ketamine. There was demonstrated the possibility that acoustic evoked responses from the somatosensory cortex can be used as an indication of the level of ketamine anesthesia. 24 references. (Author abstract modified)

002363 Dafny, Nachum. Department of Neurology and Anatomy, University of Texas Medical School, Texas Medical Center, Houston, TX 77025 **Neurophysiological approach as a tool to study the effects of drugs on the central nervous system: dose effect of pentobarbital.** Experimental Neurology. 59(2):263-274, 1978.

To explore a neurophysiological methodology for the study of drug central nervous system effects, average sensory evoked responses were recorded simultaneously from the inferior colliculus, mesencephalic reticular formation, nucleus ventralis lateralis thalami, ventromedial hypothalamus, caudate nucleus, and somtatosensory cortex of 16 freely behaving rats after pentobarbital administration. Several doses of pentobarbital were used; the responses observed were related to the dosage of the barbiturate and the time after injection. Effective doses of pentobarbital caused changes in the evoked responses in all animals and in all six structures. Dependable biphasic changes were observed; low doses increased and high doses attenuated the evoked potentials. The degree of attenuation was different between structures. Use of the same techniques and preparation with different drugs demonstrates different patterns of drug induced alterations, indicating that this technique detects specific effects of drugs on the central nervous system. The role of the reticular formation as the primary site of barbiturate action is discussed. 20 references. (Author abstract modified)

002364 Glennon, R. A.; Martin, B.; Johnson, K. M.; End, D. Dept. of Pharmaceutical Chemistry, Medical College of Virginia, VA Commonwealth Univ., Richmond, VA 23298 **7,N,N-trimethyltryptamine: a selective inhibitor of synaptosomal serotonin uptake.** Research Communications in Chemical Pathology and Pharmacology. 19(1):161-164, 1978.

7,N,N-Trimethyltryptamine (TMT) was synthesized and evaluated as an inhibitor of synaptosomal biogenic amine uptake in rat forebrain homogenates. In addition to inhibiting 3H-serotonin uptake, TMT appears to be quite selective and is much less potent in blocking either 3H-norepinephrine or 3H-dopamine uptake. Adult male Wistar rats, previously trained to a constant, high level of escape performance in a two compartment shuttlebox, were administered the drug i.p. and the number of successful avoidance and the number of shocks delivered was recorded. It is suggested that TMT might find application as a biochemical tool to further the understanding of the mechanism of action of antidepressant agents. 12 references. (Author abstract modified)

002365 Haber, Suzanne; Barchas, Patricia R.; Barchas, Jack D. Dept. of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305 **Effects of amphetamine on social behaviors of rhesus macaques: an animal model of paranoia.** In: Hanin, I., Animal models in psychiatry and neurology. Elmsford, N.Y., Pergamon Press, 1977. 499 p. (p. 107-114).

In a paper presented at a workshop on animal models in psychiatry and neurology held in Rockville, Maryland, in June 1977, an animal model of paranoia based on studies of the effects of chronic administration of amphetamine on the social behaviors of rhesus macaques is presented. Behavioral data was obtained for each member of two colonies of monkeys; only one member of each colony at a time received amphetamine daily while the remainder received saline. Three major amphetamine induced alterations in social and individual behaviors in the colonies were compatible with behaviors associated with amphetamine-induced paranoia in humans. A monkey treated with the drug: 1) appeared more tense in its posturing and showed increased orientation to the noises and movements of the others; 2) increased its association with one member of the colony while isolating itself from the remaining members; and 3) displayed marked increases in agonistic behaviors. It is suggested that although the linguistic subtleties of human paranoia are not present in this model, many of the

behavioral analogues are present. Moreover, drugs which ameliorate (antipsychotic drugs), exacerbate (L-DOPA), or have no effect (antianxiety agents) on amphetamine induced behaviors associated with threat in humans have the same effects in the primate model, thereby giving strength to the model. 19 references.

002366 Hanin, I.; Usdin, E. University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15261 **Animal models in psychiatry and neurology.** Elmsford, N.Y., Permagon Press, 1977. 499 p. $40.00.

The proceedings of a workshop on animal models in psychiatry and neurology held in Rockville, Maryland, in June 1977, are presented. Animal models of psychoses, affective disorders, anxiety, aggression, human cognitive processes, paranoia, dyskinesia, epilepsy, hyperactivity, Huntington's disease, subclinical brain-damage, and myoclonus are discussed in relation to: 1) biochemical, physiological, or neural correlates of various behaviors and/or disorders; 2) methodology and other factors affecting the production of the animal models; and 3) the usefulness of the models in evaluating the therapeutic efficacy and/or side-effects of psychoactive drugs including antidepressants, antipsychotic drugs, and antianxiety agents. Specific topics presented include: 1) the physiology of operant behavior; 2) the significance of sex, age, and species differences and nutritional status in the production of the various animal models; 3) qualities needed for an animal model of receptor sensitivity modification; 4) electroencephalogram sleep correlates of depression; 5) biogenic amine metabolism in the aggressive mouse killing rat; 6) a biochemical analysis of strain differences in narcotic action; 7) correlations between the effect of kainic acid lesions on muscarinic cholinergic receptor binding in Huntington's disease; 8) tardive dyskinesia and antipsychotic drugs; 9) cardiovascular toxicity of tricyclic antidepressants; and 10) the relevance of receptor binding methodology for the therapeutic and side effects of psychotropic drugs.

002367 Hutchinson, Ronald R. Foundation for Behavioral Research, Augusta, MI **Analysis and chemical control of negative affect.** Psychopharmacology Bulletin. 14(1):66, 1978.

A summary of an ongoing research project on the analysis and chemical control of negative affect in laboratory animals is presented. Techniques are being developed to measure negative affect states (including flight, fight, and freezing reactions) and the effects of several chemicals on these states. In addition, the behavioral addictive process and state produced by nicotine is being studied. A standard repetitive shock delivery session is used to explore functional interactions between cardiovascular and motor responses which are indices of escape, avoidance, and aggression reactions in squirrel monkeys.

002368 Ljungberg, Tomas. Department of Histology, Karolinska Institutet, S-10401 Stockholm, Sweden **Reliability of two activity boxes commonly used to assess drug induced behavioural changes.** Pharmacology Biochemistry and Behavior. 8(2):191-195, 1978.

To determine the reliability of the Animex activity meter and a photocell cage to assess drug induced behavioral change rats were given different drug treatments known to affect central catecholamine neurotransmission and to induce different types of behavioral changes which were recorded simultaneously by the two activity boxes. All animals were also visually observed simultaneously with the automatic recordings. It was found that the two activity boxes reflected the behavioral changes differently and that the results from the two boxes were not correlated. When comparing the observations with the automatic recordings it was found that some clearly observable changes in behavior were not reflected as changes in the automatic recordings and conversely that increases or decreases in the recorded motor activity were not always related to any particular changes in behavior. Motor activity is considered to be an undescriptive measure consisting of an artificial summation of those components of behavior that affect the movement-detecting device in the particular box which is used. 17 references. (Author abstract)

002369 McLean, J. R.; Parker, R. B.; Coughenour, L. L. Dept. of Pharmacology, Warner-Lambert/Parke-Davis Pharmaceutical Research Div., 2800 Plymouth Rd., Ann Arbor, MI 48106 **Effect of an antipsychotic and other classes of drugs on spontaneous locomotor activity and neurotoxicity in mice.** Pharmacology Biochemistry and Behavior. 8(1):97-99, 1978.

To develop a procedure for evaluating the potential antipsychotic activity of selected drugs, quantitative estimates were made of the effects of several classes of drugs on spontaneous locomotor activity and neurotoxicity in mice. Clinically effective antipsychotic agents had a more selective action on spontaneous activity than other classes of drugs with the exception of clonidine and a related compound. Results indicate that, unless clonidine has some as yet undetermined antipsychotic effect, inhibition of the conditioned avoidance response and spontaneous activity may not predict antipsychotic activity with this class of compounds. Generally, measurements of spontaneous activity and neurotoxicity are considered useful in selecting compounds for study as potential antipsychotic agents. 15 references. (Author abstract modified)

002370 Porsolt, Roger D.; Anton, Guy; Blavet, Nadine; Jalfre, Maurice. Centre de Recherche Delalande, 10, rue des Carrieres, F-92500 Rueil-Malmaison, France **Behavioural despair in rats: a new model sensitive to antidepressant treatments.** European Journal of Pharmacology (Amsterdam). 47(4):379-391, 1978.

A new model sensitive to antidepressant treatments which is based on behavioral despair in rats is presented. Rats forced to swim in a cylinder from which they cannot escape will, after an initial period of vigorous activity, adopt a characteristic immobile posture which can be readily identified. Immobility was reduced by various clinically effective antidepressant drugs at doses which otherwise decreased spontaneous motor activity in an open field. Antidepressants could thus be distinguished from psychostimulants which decreased immobility at doses which increased general activity. Anxiolytic compounds did not affect immobility whereas major tranquilizers enhanced it. Immobility was also reduced by electroconvulsive shock, REM sleep deprivation and enrichment of the environment. It is concluded that immobility reflects a state of lowered mood in the rat which is selectively sensitive to antidepressant treatments. Positive findings with atypical antidepressant drugs such as iprindole and mianserin suggest that the method may be capable of discovering new antidepressants hitherto undetectable with classical pharmacological tests. 63 references. (Author abstract modified)

002371 Sanger, D. J.; Blackman, D. E. Department of Psychology, University College, P.O. Box 78, Cardiff CF1 1XL, Wales **A variable-interval punishment procedure for assessing anxiolytic effects of drugs.** Psychological Reports. 42(1):151-156, 1978.

A variable interval punishment procedure for assessing anxiolytic effects of drugs is described. The procedure was designed to reduce previous interpretive difficulties by: 1) maintaining the same schedule of positive reinforcement during both nonpunishment and signaled punishment schedule components; 2) ensuring that food and shock were not invariably associated; 3) using a procedure in which increases in punished responding do not lead to large increases in reinforcement or shock frequency; and 4) making shock delivery less predictable during the punishment schedule. In an experiment with 3 rats, chlordiazepoxide and amobarbital were found to produce dose related decreases in the suppression of responding produced by punishment. 11 references. (Author abstract modified)

002372 Sanghvi, I. S.; Gershom, S. U.S.V. Pharmaceutical Corporation, 1 Scarsdale Road, Tuckahoe, NY 10707 **Animal test models for prediction of clinical antidepressant activity.** In: Hanin, I., Animal models in psychiatry and neurology. Elmsford, N.Y., Pergamon Press, 1977. 499 p. (p.151-169).

In a paper presented at a workshop on animal models in psychiatry and neurology held in Rockville, Maryland, in June 1977, animal models for the prediction of clinical antidepressant action are reviewed, including: 1) antagonism of the effects of reserpinelike drugs; 2) potentiation of phenethylamines; 3) monoamine oxidase inhibition; 4) Sidman continuous avoidance procedure; and 5) behavioral tests. Special emphasis is placed on a procedure in which the potentiation of yohimbine induced behavioral and cardiovascular changes in the conscious dog is measured. The results of studies using this system to evaluate the antidepressant effects of 4-phenyl-bicyclo(2,2,2)octan-1-amine hydrochloride monohydrate; N-acetonyl-N,N-dimethylbinzylammonium chloride; amphetamine; N,N-dimethyl-1-phenylindene-1-ethylamine; cocaine; 5-hydroxytryptophan; L-DOPA; lithium; thyrotropin releasing hormone; and iprindole are briefly reviewed. It is concluded that no single test is reliable for the prediction of antidepressant activity across a wide range of compounds tested. It is suggested that combined use of several of the tests reviewed may serve as preliminary tests for the prediction of probable antidepressant activity. 65 references.

002373 Schwarz, R. D.; Stein, J. W.; Bernard, P. Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, NJ 07901 **Rotometer for recording rotation in chemically or electrically stimulated rats.** Physiology & Behavior. 20(3):351-354, 1978.

An improved rotometer is described which accurately records circling behavior (rotation) in rats with an imbalance of the nigrostriatal pathways. Results of circling induced by apomorphine in rats with unilateral 6-hydroxydopamine lesions of the substantia nigra and circling elicited by electrical stimulation of the nigrostriatal pathway are presented. A representative drawing and a logic circuit schematic of the device are included. 8 references. (Author abstract modified)

002374 Siew, Chakwan; Goldstein, Dora B. American Dental Association Health Foundation, 211 East Chicago Avenue, Chicago, IL 60611 **Osmotic minipumps for administration of barbital to mice: demonstration of functional tolerance and physical dependence.** Journal of Pharmacology and Experimental Therapeutics. 204(3):541-546, 1978.

To demonstrate the utility of an implantable osmotic minipump capable of maintaining constant barbiturate blood levels resulting in a state of functional tolerance and physical dependence, sodium barbital was administered to mice at a constant rate by pumps implanted subcutaneously. Each pump delivered approximately 0.25mg/hr. With two pumps per mouse, blood barbital levels of 20 to 30 micrograms/ml could be maintained for various periods. Barbital was assayed by gas chromatography. Functional tolerance was shown by a significant decrease in sleep time after a challenge dose of barbital administered 24 hours after withdrawal. Physical dependence was demonstrated by withdrawal hyperexcitability as measured either with pentylenetetrazol or by convulsions elicited by handling. 16 references. (Author abstract modified)

CLINICAL PSYCOPHARMACOLOGY

07 EARLY CLINICAL DRUG TRIALS

002375 Amin, M. M.; Ban, T. A.; Lehmann, H. E.; Khan, P. Division of Psychopharmacology, Dept. of Psychiatry, McGill Univ., Montreal, Canada **Viloxazine in the treatment of depression: psychophysical measures and clinical response.** Psychopharmacology Bulletin. 14(1):33-35, 1978.

A paper read at a colloquium on clinical trials with antidepressants, organized by the Division of Psychopharmacology of McGill University and held at Pointe Claire, Quebec, June 1977, on psychophysical measures and clinical response with viloxazine, a bicyclic tetrahydroxine compound, in the treatment of depression is presented. In an 8 week, uncontrolled clinical trial in ten depressed psychiatric patients, viloxazine in the dosage of 100 to 300mg per day was found to have significant antidepressant properties, particularly on the retarded depression factor of the Hamilton Psychiatric Rating Scale for Depression (HAM-D). This is in keeping with its primary action in blocking norepinephrine reuptake. Statistically significant improvement was also noted on tapping speed of the Verdun Psychophysical Test Battery (VPTB). Furthermore, while there was a tendency toward improved mental performance in more complex tasks, performance on simple tasks was seen to deteriorate in some instances. Further, viloxazine produced few side-effects. One patient showed evidence suggestive of choleostatic jaundice during week 4 of drug administration, but the liver function profile remained stable in spite of continued drug administration for the following 4 weeks. 2 references. (Author abstract modified)

002376 Amin, M. M.; Ban, T. A.; Lehmann, H. E.; Khalid, R. Division of Psychopharmacology, Dept. of Psychiatry, McGill Univ., Montreal, Canada **R-806-003-01 in the treatment of depression: plasma levels and therapeutic response.** Psychopharmacology Bulletin. 14(1):31-33, 1978.

A paper read at a colloquium on clinical trials with antidepressants, organized by the Division of Psychopharmacology of McGill University and held at Pointe Claire, Quebec, June 1977, on plasma levels and therapeutic response in the treatment of depression with R-806-003-01, a tetracyclic compound, is presented. An open, uncontrolled, 34 day clinical study was conducted to determine the therapeutic effects of R-806-003-01 in the dosage range of 5 to 30mg per day in depressed patients. Statistically significant improvement occurred on the total, retarded depression, and sleep disturbance factor scores of the Hamilton Psychiatric Rating Scale for Depression (HAM-D). A moderate degree of positive correlation occurred between plasma levels and HAM-D scores. The most frequently occurring adverse effects were akathisia, constipation, excitement/agitation, insomnia, sweating, and tremor. Nine of the ten patients showed a weight loss during the course of the clinical trial. (Author abstract modified)

002377 Becker, W.; Bockenheimer, S.; Degkwitz, R. Psychiatrische und Nervenklinik, Hauptstrasse 5, D-7800 Freiburg i. Br., Germany **/Characteristics of Tiliden-HCl (Valoron) intoxication./** Die Besonderheiten des Rauscherlebnisses unter Tilidin-HCl (Valoron). Nervenarzt (Berlin). 48(12):692-695, 1977.

The characteristics of intoxication from Tiliden-HCl (Valoron), a nonaddictive drug used with increasing frequency by addicts to replace opiates or to avoid withdrawal symptoms, was described based on studies on 13 male addicts. In contrast to pain patients, eight of the addicts experienced intoxication like that induced by heroin. Even at low oral doses, a 5 to 6 hour delirium began after 20 to 30 minutes with motor restlessness, a feeling of harmony, intense sensory perception, increased mental activity and self-confidence, loss of inhibitions, and ended with pains in limbs, depression, and sleeplessness. Eventually impotence occurs. The drug is difficult to classify and its effects vary according to application method, combination with other substances (e.g. alcohol), and predisposition of individual patients. It is concluded that Tiliden is unsuitable for withdrawal treatment, because its intoxication effects are especially frequent in addicts. 20 references. (Author abstract modified)

002378 Beckmann, H.; Frische, M.; Ruther, E.; Zimmer, R. Psychiatrische Klinik der Universitat, Nussbaumstrasse 7, D-8000 Munich 2, Germany **Baclofen (p-chlorphenyl-GABA) in schizophrenia.** Pharmakopsychiatrie/Neuro-Psychopharmakologie (Stuttgart). 10(1):26-31, 1977.

Based on reported improvement in schizophrenics given baclofen together with intermediate doses of neuroleptic drugs, a study was made of the effects of baclofen (p-chlorophenyl-GABA) alone in 21 recently hospitalized schizophrenic patients. The 11 males and 10 females were 20 to 50 yr old, with a mean age of 34 yr, and duration of illness ranged from less than 1 yr to 18 yr. Diagnoses were hebephrenic schizophrenia in 7, paranoid schizophrenia in 7, residual and deficiency schizophrenic states in 5, latent schizophrenia in 1, and schizoaffective state in 1. Patients were on placebo for at least 1 wk prior to the beginning of the study. The initial dose of baclofen was 15mg/day, and this was increased, in accordance with tolerance, to 125mg/day. The study lasted 20 days. Patients were rated every 5 days on the AMP system, and were rated at the end of the study by global clinical impression. Four patients did not complete the trial because of serious and unmanageable psychotic exacerbations. Of the remaining 17 patients, seven showed improvement, five showed no change, and nine showed deterioration. No changes in routine laboratory tests were observed. 18 references.

002379 Cesco, G.; Giannico, S.; Fabbrucci, I.; Scaggiante, L.; Montanaro, N. Divisione Malattie Apparato Respiratorio, Ospedale Civile Umberto 1, Mestre, Italy **Single-blind evaluation of hypnotic activity of chlordesmethyldiazepam in no-placebo-reactor medical patients.** Arzneimittel-Forschung (Aulendorf). 27(1):146-148, 1977.

The hypnotic effect of chlordesmethyldiazepam was studied in insomniac patients hospitalized for the treatment of various respiratory diseases. The 69 inpatients comprised 55 males and 14 females with an average age of 62. The first two nights, all patients were given placebo. A total of 33 patients did not react to the placebo, and these patients were admitted to the drug trial. The 28 men and five women were asked to estimate their onset of sleep, duration of sleep, quality of sleep, and state of awakening. Three patients had to be dropped from the trial because of daytime drowsiness. The remaining 30 patients reported sleep onset in about 30 min, duration of sleep of about 7 hr restful quality of sleep, and normal state of awakening. 21 references.

002380 Eckel, K. Abteilung fur Psychologische Physiologie, Universitat Salzburg, Akademiestrasse 26, A-5020 Salzburg, Austria **/Therapeutic effect of brain hydrolysates in depression induced disturbances of intelligence./** Therapeutische Wirkung von Gehirnhydrolysaten bei depressionsbedingten Intelligenzstorungen. Wiener Medizinische Wochenschrift (Wien). 127(2):85-88, 1977.

Studies of the treatment of endogenous depression with a combination of antidepressants and cerebral hydrolysates are reviewed. Rapid brightening of mood and improvement in cerebral performance capacity were noted, as well as improvement in memory. The other depressive symptoms also lessened following treatment. Both MAO inhibitors and tricyclic drugs were effective. The amino acid mixture acts on the metabolism of transmitter substances, which is disturbed in depression. 19 references.

002381 Fann, W. E.; Schroeder, D. H.; Mehta, N. B.; Soroko, F. E.; Maxwell, R. A. Dept. of Psychiatry, Baylor College of Medicine, Houston, TX 77030 **Clinical trial of bupropion HCl in treatment of depression.** Current Therapeutic Research. 23(2):222-229, 1978.

A single-blind clinical study of buproprion hydrochloride, a phenylaminoketone, was conducted to assess its antidepressant activity. The subjects were 11 hospitalized depressive patients, 10 of whom had been refractory to previous antidepressant medications. Pretreatment laboratory reports on all the subjects were negative for factors contraindicating participation in the study. Two patients were dropped from the study for reasons unrelated to bupropion medication. After 4 weeks of bupropion therapy, all nine subjects were improved as established by ratings on the Hamilton Psychiatric Scale and the Zung Depression Scale. There were no significant changes in laboratory data and no anticholinergic side-effects. It was concluded that buproprion appears to have antidepressant activity, and further clinical trials with buproprion in depressed patients are recommended. 4 references.

002382 Greenblatt, David J.; Shader, Richard I. Clinical Pharmacology Unit, Mass. General Hospital, Boston, MA 02114 **Prazepam, a precursor of desmethyldiazepam.** Lancet (London). No.8066:720, 1978.

The reportedly unique pharmacological action of prazepam is studied in a group of fasting volunteers. Twenty milligrams of prazepam were administered and over the next 7 days blood concentrations of desmethyldiazepam rose rapidly and fell gradually. No prazepam was present in any sample. It is concluded that prazepam is a precursor for desmethyldiazepam, and is thus not unique in its pharmacokinetic actions. 5 references.

002383 Grevert, Priscilla; Goldstein, Avram. Addiction Research Foundation, Palo Alto, CA 94304 **Endorphins: naloxone fails to alter experimental pain or mood in humans.** Science. 199(4333):1093-1095, 1978.

The effect of naloxone on stimulating endorphin receptors to alter experimental pain or mood in humans was studied. In 30 human subjects, experimental pain was produced by either ischemia or cold water immersion. In a double-blind procedure, intravenous doses of naloxone hydrochloride in saline were indistinguishable from similarly administered saline alone. There were no effects on subjective pain ratings, finger plethysmograph recordings, or responses to mood state questionnaires. It is concluded that these laboratory procedures do not activate any functionally significant pain attenuating or mood altering effect of endorphins. 17 references. (Author abstract modified)

002384 Haits, G. Psychiatric Ward of Outpatients' Department, Merenyi Gusztav Hospital, Budapest IX, Hungary **Observations on the continuous use of trioxazine.** Therapia Hungarica (Budapest). 24(4):145-147, 1976.

A followup study was done of 42 patients for whom trioxazine, a minor tranquilizer, had been prescribed 18 to 24 mos earlier. Of the 42 patients, 26 were still taking one to two tablets t.i.d. of trioxazine, three took one tablet occasionally, and 13 had discontinued the drug. Of these 13, seven became symptom free after 3 to 6 mos and six patients were changed to a more potent tranquilizer. The 26 patients still on trioxazine ranged in age from 20 to 65 yr. These included 12 males and 14 females, most of whom had a neurotic diagnosis. The patients were taking no other psychotropic drugs except for nighttime hypnotics. The 26 patients were evaluated by interview and the Taylor Manifest Anxiety Scale. Only one patient had a high score on the Taylor Anxiety Scale. Based on the interview, eight patients were symptom free, ten had mild symptoms, four showed no change in symptoms but satisfactory adaptation, and four had to be changed to a more potent drug. No drug dependence or tolerance was reported. 2 references.

002385 Legros, J. J.; Gilot, P.; Seron, X.; Claessens, J.; Adam, A.; Moeglen, J. M.; Audibert, A.; Berchier, P. Neuroendocrinology Section, Dept. of Clinical & Medical Pathology, Universite de Liege,-Sart Tilman, B-4000 Liege, Belgium **Influence of vasopressin on learning and memory.** Lancet (London). No. 8054:41-42, 1978.

In a letter to the editor, the influence of exogenous vasopressin on learning and memory in men aged 50 to 65 years old is discussed. Twenty three inpatient volunteers with minor pulmonary or gastroenterological diseases were administered 16 IU of lysine-8-vasopressin or a placebo for 3 days, and were measured with regard to weight, pulse rate, blood pressure, serum proteins, plasma sodium, urine volume and osmolality, and a battery of psychometric tests. No significant clinical or biochemical changes were noted, but patients given vasopressin performed better in tests involving attention, concentration, motor rapidity, visual retention, recognition, and recall than did controls. Whether the effect is an alteration in attention and short-term memory or whether it is an increase in memory consolidation and retrieval from long-term memory is currently being researched. 13 references.

002386 Lidberg, L.; Sternthal, V. Laboratory for Clinical Stress Research, Fack, S-10401 Stockholm, 60, Sweden **A new approach to the hormonal treatment of impotentia erectionis.** Pharmakopsychiatrie/Neuro-Psychopharmakologie (Stuttgart). 10(1):21-25, 1977.

Effects of oral synthetic oxytocin was studied in 30 males with impotentia erectionis in a placebo controlled, double-blind trial. The patients, 25 to 62 yrs old, with duration of impotence ranging from 2 mo to 120 mo, were divided into groups receiving 100 or 200 IU oxytocin p.o. t.i.d.,or placebo. Intermittent and constant symptoms were equally divided among the patients. Treatment lasted 7 wk to 18 wk, averaging 8 or 9 wk. Results, rated on the basis of sexual interest and sexual capability, showed patients receiving 300 IU oxytocin daily improved more than those receiving 600 IU. The placebo group showed the least improvement. The hormone was well tolerated, and no untoward side-effects were observed. Further observations are needed to explain the differential effect of oxytocin in a high and medium dose. 31 references.

08 DRUG TRIALS IN SCHIZOPHRENIA

002387 Berken, Gilbert H.; Stone, Melvin M.; Stone, Shirley K. Hollywood Memorial Hospital, Hollywood, FL **Methadone in schizophrenic rage: a case study.** American Journal of Psychiatry. 135(2):248-249, 1978.

A case history of a 19-year-old woman who was suffering from paranoid schizophrenia and received methadone treatment is presented to demonstrate the possible role of methadone in the management of psychotic rage. The subject's compulsion toward self-mutilation and suicide had been poorly controlled by conventional and medically accepted therapies. After securing special permission from the appropriate agencies, methadone was administered with a concurrent program of therapy and social interaction. After 40 months of treatment she was detoxified from methadone and currently receives a hypnotic and no other medication. Within 3 months after the methadone was stopped, she exhibited some minor rage responses but sucessfully handled them. It is concluded that the normalizing effect of methadone proved more satisfactory for this patient than any treatment she had previously received. Further investigation of the mechanisms and effects of narcotics in normalizing psychotic rage is recommended.

002388 Bjerkenstedt, Lars. Laboratory of Experimental Psychiatry, Dept. of Psychiatry, Karolinska Institutet, S-104 01 Stockholm, Sweden **Clinical and biochemical changes in psychotic women treated with melperone or thiothixene.** Final Report. NIMH Grant MH-27254, 1978.

The therapeutic and metabolic effects of melperone and thiothixene were compared in a double-blind experiment involving 64 psychotic women with schizophrenic symptomatology. Attempts were made to correlate therapeutic outcome with metabolic effects. It was found that: 1) both drugs equally reduced psychotic morbidity; 2) thiothixene caused greater elevations of homovanillic acid levels; 3) clinical doses of melperone appear to interfere with central noradrengic mechanisms, and 4) correlations exist between therapeutic outcome and several biochemical changes. The value of simultaneous analysis of clinical and biochemical parameters chanisms of action is noted. 56 references.

002389 Carlsson, Arvid. Department of Pharmacology, University of Goteborg, Goteborg, Sweden **Does dopamine have a role in schizophrenia?** Biological Psychiatry. 13(1):3-21, 1978.

An overview of psychopharmacological research elucidating possible biochemical/metabolic factors in schizophrenia, particularly the role of dopamine (DA) is presented. Among the topics discussed are: 1) early studies with reserpine, dopa and DA; 2) investigations into the blockade of DA and nonadrenaline (NA) receptors by neuroleptics, and results of studies of major neuroleptics; 3) the antipsychotic action of alpha-methyltyrosine and possible implications of the effects of catecholamine synthesis inhibition on schizophrenic symptomatology; and 4) the schizophrenia mimicking actions of the catecholaminergic drugs. Findings indicate that dopaminergic activity appears necessary to the induction of schizophrenic symptoms. However, whether DA plays a primary role in schizophrenia is open to question because of the complex interplay among the pacemaker/conduction, the limbic, and the extrapyramidal systems and the possible roles of other biogenic amines and amino acid or peptide transmitters. Evidence pointing to a primary DA role includes monoamine oxidase deficiency, deficient catechol-O-methyltransferase, deficient transport of transmitters or increased receptor sensitivity, and increased presynaptic DA activity. 75 references.

002390 Chouinard, Guy; Annable, Lawrence; Kropsky, Michael. Allan Memorial Institute, Pharmacology Research Unit, McGill University, Montreal, Quebec, Canada **A double-blind controlled study of pipothiazine palmitate in the maintenance treatment of schizophrenic outpatients.** Journal of Clinical Pharmacology. 18(2-3):148-154, 1978.

To examine the relative efficacy of a long-acting neuroleptic and a long-acting phenothiazine in treatment of schizophrenia, pipothiazine palmitate, a neuroleptic that can be administered intramuscularly once a month was compared with fluphenazine enanthate in the maintenance treatment of 32 schizophrenic outpatients in a 9 month double-blind controlled study. Before the trial commenced, all patients were being treated with fluphenazine enanthate. The results indicate that pipothiazine palmitate was not as potent a neuroleptic as fluphenazine enanthate. Pipothiazine appears to resemble fluphenazine enanthate in its capacity to induce parkinsonism and tardive dyskinesia. 10 references. (Author abstract modified)

002391 Chouinard, Guy; Annable, Lawrence; Kolivakis, Thomas N. L. Department of Psychiatry, McGill University, Montreal, Quebec, Canada **Penfluridol in the maintenance treatment of schizophrenic patients newly discharged from a brief therapy unit.** Journal of Clinical Pharmacology. 17(2-3):162-167, 1977.

Penfluridol, a long-acting neuroleptic that can be administered orally once a week, was compared with chlorpromazine in a 10 wk double-blind study. Patients were 29 newly discharged schizophrenics who had been hospitalized for 3 wk. The 15 men and 14 women were 19 to 60 yrs old, with a median age of 35. Eight patients did not complete the study, mostly because of side effects, leaving 11 patients in the penfluridol group and 10 patients in the chlorpromazine group. Penfluriodol dosage was 40mg the first wk, 80mg the second wk, and 120mg thereafter, while chlorpromazine was given 300mg/day the first wk, 600mg/day the second wk, and 900mg/day thereafter. In half the patients the dosage had to be reduced because of side effects. Patients were assessed on the Inpatient Multidimensional Psychiatric Rating Scale, and a 7 point Clinical Global Impression scale. There was no difference in efficacy between the two drugs. Laboratory tests, blood counts, and urinalysis were within normal limits. Penfluridol caused more extrapyramidal effects while chlorpromazine caused more drowsiness. Two patients on penfluridol developed depression. 9 references.

002392 Dencker, Sven J.; Frankenberg, Ken; Lepp, Marje; Lindberg, Dick; Malm, Ulf. Dept. II, Lillhagen Mental Hospital, Box 3005, S-42203 Hisings Backa, Sweden **Three years' maintenance neuroleptic treatment in schizophrenia -- before and beyond.** Acta Psychiatrica Scandinavica (Kobenhavn). 57(2):103-114, 1978.

Changes in psychopathology and side-effects of a group of 67 chronic schizophrenics treated with two depot neuroleptics, fluphenazine decanoate and pipotiazine palmitate, given monthly over a 3 year period are reported. After 3 years 36 out of 67 patients were still on the same depot neuroleptic. Improvement in social functioning and work level and significant symptom reductions were found after 1 year of comprehensive therapy and 2 years of only drug therapy. Side-effects were low in frequency and quality. Results confirm the clinical value of long-term maintenance treatment with neuroleptics. Possibilities of improving aftercare and outpatient treatment beyond medication alone are discussed. 24 references. (Author abstract modified)

002393 Dencker, Sven J.; Frankenberg, Ken; Lepp, Marje; Lindberg, Dick; Malm, Ulf. Dept. II, Lillhagen Mental Hospital, Box 3005, S-42203, Hisings Backa, Sweden **How schizophrenic patients change during 3 years' treatment with depot neuroleptics.** Acta Psychiatrica Scandinavica (Kobenhavn). 57(2):115-123, 1978.

Symptom changes in schizophrenics during long-term (3 years) treatment with neuroleptics are analyzed according to S-scale, BPRS scale, and Hamilton's scale for depressive symptoms. Four factors were found to explain the variance satisfactorily: one comprising psychopathological symptoms specific for schizophrenia, one relating to contact disturbances, one psychomotor activity and one representing neurotic symptoms. Analysis of these factors revealed certain differences between the treatment groups over time and demonstrated the effect of combination of psychotherapy and neuroleptic drugs in a subgroup of patients. Ways this type of analysis of treatment results might contribute to improving knowledge of rehabilitation of schizophrenic patients and help to draw up guidelines for selection of suitable measures, are discussed. 8 references. (Author abstract modified)

002394 Ekiert, Halina; Gogol, Zofia; Welbel, Leszek; Kazubska, Maria. Instytut Psychoneurologiczny, 1/9 Sobieskiego al., Warszawa 09-957, Poland **/EEG records and the effects of phenothiazine treatment in patients with paranoid schizophrenia./** Zapis EEG a wynik leczenia fenotiazynami chorych na schizofrenie paranoidalna. Psychiatria Polska (Warszawa). 11(3):325-333, 1977.

A total of 51 patients, aged 16 to 57 (33 male and 18 female), who were diagnosed as paranoid schizophrenic and received various phenothiazine derivatives, were investigated to make a parallel evaluation of their mental state and their EEG records. Mental state was assessed with a symptom inventory. The EEG records were assessed visually. Attempts were made to find out whether the EEG records corresponded to the clinical state, and to determine any possible prognostic signs in the neuroleptic therapy. Varying improvement was found in about 80% of patients receiving phenothiazine. The EEG records for most of the patients showed changes consisting chiefly in slowing of the alpha-rhythm and occurrence and activation of slow-waves, which phenomena were particularly marked when high phenothiazine doses were used. Changes in the EEG records were found not to coincide with the treatment effects. It is suggested that EEG records had little prognostic value in relation to the therapy. 27 references. (Journal abstract modified)

002395 Ekiert, Halina; Gogol, Zofia; Welbel, Leszek. Instytut Psychoneurologiczny, Zaklad EEG/EMG, Al. Sobieskiego 1/9, 02-957 Warszawa, Poland **/Effects of flupenthixol on the clinical state and EEG of schizophrenics./** Wplyw flupentiksolu na stan kliniczny i obraz EEG u chorych na schizofrenie. Psychiatria Polska (Warszawa). 11(1):7-14, 1977.

A study of the effects of fluphenthixol on the clinical state and EEG recordings of schizophrenic patients is presented, based on examination of 20 patients (6 men and 14 women), aged 16 to 58, with duration of diseases from 3 to 25 years. Flupenthixol was given 4mg to 8mg p.o. for 4 to 6 weeks. In some patients additional drugs had to be given because indications (levopromazine, hydroxyzine, parkopan). Influence of the drug on the EEG was followed throughout the treatment. Results suggest that best effects with this drug are obtained in patients with communication problems, social maladjustment, and thought and mood disturbances. Modification of the EEG was significantly more frequent in patients who responded favorably to treatment. 20 references. (Journal abstract modified)

002396 Falloon, I.; Watt, D. C.; Shepherd, Michael. Institute of Psychiatry, De Crespigny Park, London SE5 8AF, England **A comparative controlled trial of pimozide and fluphenazine decanoate in the continuation therapy of schizophrenia.** Psychological Medicine (London). 8(1):59-70, 1978.

A comparative trial of pimozide and fluphenazine decanoate in the treatment of schizophrenia was carried out to assess the relative efficacy of the two compounds in respect of 1) relapse and rate of relapse of florid schizophrenic symptomatology; 2) depressive symptomatology; 3) admission to hospital; 4) adverse effects, frequency and severity; 5) regularity of medication; and 6) social functioning. The subjects were schizophrenic patients returning to the community following hospital treatment of an acute schizophrenic episode. Results indicated that oral pimozide was clinically as effective as depot injections of fluphenazine decanoate in the continuation therapy of schizophrenic outpatients and was associated with fewer side-effects. A third of the schizophrenic patients who entered the trial relapsed during the 12 months, which is a substantially higher proportion than those reported in studies of long-acting phenothiazines. The most striking feature about the readmitted schizophrenic patients, however, was that more than half of them were completely free of schizophrenic symptoms. Relapse was most frequently equated with an exacerbation of psychiatric symptoms already present, particularly depression. 29 references.

002397 Gillin, J. Christian; Stoff, David M.; Wyatt, Richard Jed. Laboratory of Clinical Psychopharmacology, Div. of Special Mental Health Research, NIMH, St. Elizabeths Hospital, Washington, DC 20032 **Transmethylation hypothesis: a review of progress.** In: Lipton, M., Psychopharmacology: a generation of progress. New York, Raven Press, 1978. 1731 p. (p. 1097-1112).

The transmethylation hypothesis of schizophrenia (that schizophenia results from the endogenous synthesis of methylated hallucinogenic agents) is reviewed, and the status of four substances as the abnormally methylated schizotoxin is evaluated. These substances are N,N-dimethyltryptamine (DMT), 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), 5-hydroxy-N,N-dimethyltryptamine (bufotenine), and 34-dimethoxyphenylethylamine (DMPEA). Topics discussed include: activity of methylating enzymes in schizophrenic patients, presence of methylated schizotoxins in schizophrenic patients, administration of methylated amines to man, treatment with methyl acceptors, animal behavioral studies, chronic and acute effects on conditioned and unconditioned animal behavior, and drug interaction studies in animals. 114 references.

002398 Hansell, Norris. Champaign County Mental Health Center, Urbana, IL 61801 **Services for schizophrenics: a lifelong approach to treatment.** Hospital & Community Psychiatry. 29(2):105-109, 1978.

A lifelong approach to treatment for schizophrenics is advocated, arguing that the crisis intervention/social programming orientation of mental health services in the 1960's resulted in an unwarranted emphasis on the single episode user of services and lack of interest in patients such as schizophrenics who needed repeated services. Recent studies are cited which indicate that many cases of schizophrenia have a heritable biological component and respond well to neuroleptic medication. For effective outpatient treatment of schizophrenics who might otherwise be repeated users of

hospital service, a program of continuous, or nearly continuous, neuroleptic medication combined with counseling and social and crisis services is recommended. It is suggested also that the patient should be educated to take a role in self-regulation of medication within a prescribed range which would thus improve safety, precision, and reliability. 25 references. (Author abstract modified)

002399 Iversen, Leslie L.; Iversen, Susan D.; Snyder, Solomon H. Department of Pharmacology, University of Cambridge, Cambridge, England **Neuroleptics and schizophrenia.** Handbook of Psychopharmacology, Vol. 10. New York, Plenum Press, 1978. 250 p. $25.00.

The biochemical, pharmacological and clinical aspects of the use of neuroleptics to treat schizophrenia are reviewed and discussed. Topics presented include: 1) structure/activity relationships of the butyrophenones and diphenylbutylpiperidines; 2) biochemical effects of neuroleptic drugs at the dopamine receptor; 3) behavioral effects of neuroleptics in rats, mice, cats, guinea pigs, dogs and monkeys as well as humans; 4) the efficacy of various antipsychotic drugs and treatment regimens (including combination therapy with multiple drugs, drugs plus somatic therapy, and drugs plus psychotherapy or social treatments); 5) neuroleptic induced tardive dyskinesia and related neurologic disorders; 6) the pharmacology of reserpine; and 7) neurotransmitter theories of schizophrenia.

002400 Lange, Ehrig; Konig, Liesbeth. Neurol-Psych. Klin. Medizinische Akademie "Carl Gustav Carus" Dresden, Fetscherstrasse 74, DDR-8019 Dresden, Germany **/Fluphenazine depot (Lyorodin depot) -- soon in production in the DDR?/** Fluphenazin-Depot (Lyorodin-Depot) -- demnachst in DDR-Produktion? Psychiatrie, Neurologie und medizinische Psychologie (Leipzig). 29(8):498-499, 1977.

A test of a brand of fluphenazine, Lyorodin depot, manufactured in East Germany, is reported. Chronic schizophrenics (N=104) were treated for 2 to 12 months with dosages of 12.5to 50mg at 1 to 4 week intervals. Lyorodin depot was found to be identical with the previously imported product, Lyogen depot, in regard to tolerance, therapeutic effect, and duration of action. The advantages of long-acting drug form in the treatment of schizophrenics is discussed.

002401 Lonowski, D. J.; Sterling, F. E.; Kennedy, J. C. Central Louisiana State Hospital, Pineville, LA 71360 **Gradual reduction of neuroleptic drugs among chronic schizophrenics: a double-blind controlled study.** Acta Psychiatrica Scandinavica (Kobenhavn). 57(2):97-102, 1978.

Effects of gradual reductions of neuroleptic drugs among hospitalized chronic schizophrenics while maintaining daily administration schedules were evaluated in a double-blind study. Neuroleptic drugs were gradually reduced from 25 hospitalized chronic schizophrenics while 23 such patients were maintained on matched dosages of neuroleptics. After 15 weeks, 74% of the drug reduced subjects and 80% of the drug maintained subjects were rated to have decompensated. Drug reduced patients decompensated while receiving a mean of 75mg equivalent of chlorpromazine. Clinical stability was obtained at 150mg equivalent of chlorpromazine. Of the drug reduced patients 26% showed no signs of clinical relapse at the end of the 15 week trial and were receiving a mean of 8mg equivalent of chlorpromazine. Results suggest that gradual and successive reductions in maintenance antipsychotic drugs can be implemented with minimal risk to the clinical status of the chronic mental patient. 7 references. (Author abstract modified)

002402 Marriott, Peter; Hiep, Albert. Royal Park Psychiatric Hospital, Melbourne Clinic, 130 Church Street, Richmond, Victoria 3121, Australia **Drug monitoring at an Australian depot phenothiazine clinic.** Journal of Clinical Psychiatry. 39(3):206-207, 211-212, 1978.

To examine current trends in an Australian outpatient clinic for schizophrenics, fluphenazine decanoate dosage, dosage intervals, and antiparkinsonian drug prescribing patterns were monitored. A survey of dosages given 167 patients during June 1973 indicated that most dosages ranged between 6.25 and 37.5mg: 16 males and seven females received dosages of 50mg or more. A further study of 192 patients indicated that almost 80% of the sample was between the ages of 21 and 50; and that the mean dosage was 29.5mg, with mean dosage levels for males being higher than those for females. A still later study of 131 patients indicated a further reduction in dosage levels, longer treatment times for females than for males, and a significant reduction in rehospitalization rates for both male and female patients in the 2 year period since initiation of the outpatient program. Intervals between injections range between 1 and 8 weeks for the vast majority of patients in remission. In June 1973, antiparkinsonian drugs were being prescribed for 57.59% (96) of the total patient population; by 1975 30.5% (115) of the total patient population were receiving such drugs. 15 references.

002403 Nestoros, J. N.; Ban, Thomas A.; Lehmann, H. E. Division of Psychopharmacology, Department of Psychiatry, McGill University, Montreal, Quebec, Canada **Transmethylation hypothesis of schizophrenia: methionine and nicotinic acid.** International Pharmacopsychiatry (Basel). 12(4):215-246, 1977.

The transmethylation hypothesis of schizophrenia was reviewed with considerations that large doses of methionine when combined with a monoamine oxidase inhibitor lead to exacerbation of psychotic symptoms in a significant percentage of chronic schizophrenic patients. Large doses of methionine, especially when combined with an inhibitor of monoamine oxidase (MAO), lead to striking exacerbation of the psychotic symptoms in a significant percentage of chronic schizophrenic patients. This finding is interpreted as the result of the methionine induced qualitative and quantitative abnormal methylation reactions, which exacerbate the postulated biochemical reactions involved in the etiology of schizophrenia, but it is suggested it could also represent behavioral effects of methionine induced toxic psychosis unrelated to schizophrenia. Nicotinic acid in doses of 3000mg/day was not found to impair the body's capacity to methylate in normal human subjects and could neither prevent nor counteract the psychopathology induced in schizophrenic patients by the combined administration of methionine and tranylcypromine. 44 references.

002404 O'Connell, Ralph A.; Lieberman, Jeffrey A. Dept. of Psychiatry, St. Vincent's Hospital & Medical Center, New York, NY **Parenteral loxapine in acute schizophrenia.** Current Therapeutic Research. 23(2):236-242, 1978.

Parental loxapine was evaluated in 10 acute schizophrenic patients in an open study, involving an intramuscular phase for 2 to 5 days, followed by a 2 to 4 week oral phase. Loxapine was rapidly effective in controlling acute psychotic symptoms. Significant improvement was noted on the Brief Psychiatric Rating Scale and Clinical Global Impression. Most common side-effects were sedation and extrapyramidal symptoms. It was concluded that parental loxapine appears to be safe and effective for the treatment of acute schizophrenic patients. 11 references. (Author abstract modified)

002405 Owens, D. G. Cunningham. Clinical Research Centre, Harrow, England **Dopamine and schizophrenia.** Nursing Mirror (London). 146(5):23-26, 1978.

The cerebral neurotransmitter dopamine, its possible relationship to the etiology of schizophrenia and the mode of action of neuroleptic drugs is reviewed. Dopamine blockade is central to antipsychotic activity; all known effective antipsychotic agents are dopamine blocking agents and though other properties may vary, there is no effective antischizophrenic agent which does not have this property. However, there is much evidence against the view that schizophrenia, therefore, is characterized by an excess of dopamine activity. The implication of the work summarized is that schizophrenia is a biological phenomenon amenable to pharmacological treatment. 3 references.

002406 Owens, David. San Diego County Mental Health Services, Box 3067, San Diego, CA 92103 **The use of fluphenazines in a continuing-care program.** Hospital & Community Psychiatry. 29(2):115-118, 1978.

Experience in using long-acting injectable fluphenazines with chronic schizophrenic patients in a continuing-care program in San Diego County is described. The drug was found to be long lasting in therapeutic effect, and less likely than other drugs to produce serious side-effects, particularly tardive dyskinesia. In addition, use of injectables makes it possible to avoid depending on untrained operators of residential facilities to see that the patients take their drugs. It is suggested that maintaining patients on low doses of long-acting injectables at 1 to 3 month intervals can be less costly than the smallest daily oral dose of any antipsychotic drug. 1 reference. (Author abstract modified)

002407 Simpson, George M.; Cooper, Thomas B.; Lee, J. Hillary; Young, Michael A. Rockland Research Institute, Orangeburg, NY 10962 **Clinical and plasma level characteristics of intramuscular and oral loxapine.** Psychopharmacology (Berlin). 56(2):225-232, 1978.

The intramuscular and oral forms of loxapine succinate, a new antipsychotic agent, were compared in their clinical, side-effect, and blood level characteristics in ten hospitalized chronic schizophrenic patients. The first phase of the study determined sedation threshold; this dose was essentially the same for the two forms. Continuous administration of the two forms using the individualized sedation threshold dosage also failed to indicate any clinical or side-effect differences in the two forms. The blood level characteristics, however, did differ between the two forms. The kinetic studies indicated that there was a larger area under the loxapine curve with the intramuscular form than with the oral form, while the 8-OH loxapine area was larger with the oral form. The steady state studies also showed that the i.m. form had higher loxapine levels than the oral form. The significance of these findings, both clinically and in terms of the relative activity of loxapine and its metabolites, is discussed. 11 references. (Author abstract)

002408 Siris, Samuel G.; van Kammen, Daniel P.; De Fraites, Emanuel G. Dept. of Mental Hygiene, NY State Psychiatric Institute, New York, NY **Serum prolactin and antipsychotic responses to pimozide in schizophrenia.** Psychopharmacology Bulletin. 14(1):11-14, 1978.

A paper read at the annual meeting of the New Clinical Drug Evaluation Units of NIMH in Key Biscayne, FL, May 1977, on serum prolactin and antipsychotic responses to pimozide in schizophrenia is presented. Eleven men and six women schizophrenics participated in a double-blind study, and were found to have significant positive correlations between prolactin increment and pimozide dose and between prolactin increment and psychosis improvement. Results suggest either that pimozide differs from haloperidol in its relative effects on the proposed tubero/infundibular prolactin regulatory and mesolimbic/mesocortical therapeutic dopaminergic systems, or that the milligram potency of pimozide has been overestimated. 19 references.

002409 Tan, E. K.; Carr, John E. no address **Psychiatric sequelae of Amok.** Culture, Medicine and Psychiatry. 1(1):59-67, 1977.

Psychiatric sequelae of Amok, an acute outburst of unrestrained violence associated with homicidal attacks, preceded by a period of brooding and ending with exhaustion and amnesia, found in the Malaysian culture, are analyzed. Sixteen cases of Amok were intensively studied and interviewed in the Security Ward of Hospital Bahagia, Ulu Kinta, Malaysia. Psychiatric sequelae were studied in terms of duration of hospitalization, relapse rate, progress on the ward, and sophistication regarding the concept of Amok. There was little difference in the hospital course of sophisticated (knowledgeable about Amok) versus naive patients. It was found that some patients followed the course of a chronic relapsing schizophrenic illness despite phenothiazine medication, whereas one group remained symptom free over an average of 16 years' hospitalization, and in the case of sophisticated patients, without medication. It is postulated that the latter group represents a decreasing cohort of classical cases of Amok, a culture bound syndrome of some degree of specificity in its etiology, nature of attack, and sequelae, which is being replaced by variant forms in which psychopathology has increasingly intruded. 15 references.

002410 Van der Velde, Christiaan D. A. Ribicoff Research Center, Norwich Hospital, Norwich, CT 06360 **Efficacy of loxapine hydrochloride intramuscular (Loxitane-IM) in acute schizophrenia.** Current Therapeutic Research. 23(3):367-374, 1978.

The efficacy of intramuscular administration of loxapine preceding its oral administration was investigated in a 4 week study using 21 schizophrenics who were hospitalized with acute symptomatology. Psychiatric ratings on the Brief Psychiatric Rating Scale, the Systematic Nurses' Observation of Psychopathology, and the Clinical Global Impressions Scale reflected rapid improvement on many items and factors during the parenteral phase, followed by sustained or further improvement during the oral phase. The most frequently observed side-effects were mild extrapyramidal symptoms throughout the study, while sedation was most apparent during the parenteral phase. These findings indicate that the initial intramuscular administration of loxapine is a useful approach in the treatment of acute schizophrenia. 14 references. (Author abstract)

002411 Wittkopp, T. A. Dunn County Health Care Center, Menomonie, WI **Evaluation of loxapine hydrochloride oral concentrate (Loxitane C) in acute schizophrenia.** Journal of Clinical Psychiatry. 39(2):154-157, 1978.

The efficacy and safety of loxapine hydrochloride in a concentrated solution was studied in patients with acute schizophrenia. In an open study of 4-weeks duration, both an oral liquid concentrate formulation of loxapine hydrochloride and capsules of loxapine succinate were administered to 11 acutely disturbed schizophrenic patients. Optimal dosage levels

achieved with the concentrate proved satisfactory with the capsules. Efficacy evaluation with the Brief Psychiatric Rating Scale, Systematic Nurses' Observation of Psychopathology, and Clinical Global Impressions indicated rapid improvement with concentrate administration and continued improvement with capsule administration. All but two side-effects were extrapyramidal or sedative, all but one were mild or moderate in severity, and the frequency was similar with the two formulations. Cardiovascular and clinical laboratory findings remained essentially unchanged with both formulations. 8 references. (Author abstract modified)

002412 Woggon, B.; Dick, P.; Fleischhauer, H. J.; Gmur, M.; Gruber, G.; Angst, J.; Heimann, H. Forschungsdirektion, Psychiatrische Universitatsklinik, CH-8000 Zurich, Switzerland **/Comparison of the effects of pipothiazine palmitate and fluphenazine decanoate in a multicenter double-blind trial./** Wirkungsvergleich von Pipothiazinpalmitat und Fluphenazindecanoat: Ergebnisse einer multizentrischen klinischen Doppelblindprufung. International Pharmacopsychiatry (Basel). 12(4):193-209, 1977.

Fluphenazine decanoate and pipothiazine palmitate were compared concerning their effect and side-effects by treating 61 schizophrenic patients for up to 6 months in a multicenter double-blind trial. Pipothiazine palmitate was injected every fourth week and fluphenazine decanoate every third week. The most often applied dosage was 100mg pipothiazine palmitate and 25 or 37.5mg fluphenazine decanoate. Data analysis of the AMP system at the symptom level showed the better antipsychotic effect of pipothiazine palmitate. A comparison between the two groups by means of analysis of covariance at the syndrome level showed no statistical significant difference between the effects of fluphenazine decanoate and pipothiazine palmitate. 9 references. (Author abstract modified)

002413 Woodrow, Kenneth M.; Reifman, Ann; Wyatt, Richard Jed. Department of Psychiatry, Stanford University Medical School, Stanford, CA 94305 **Amphetamine psychosis -- a model for paranoid schizophrenia?** In: Haber, B., Neuropharmacology and Behavior. New York, Plenum Press, 1978. 223 p. (p. 1-22).

The strengths and weaknesses of amphetamine induced psychosis as a model for paranoid schizophrenia are reviewed. Differences and similarities between amphetamine psychosis and paranoid schizophrenia based on case reports and on experimental induction studies in humans are discussed. Possible biochemical mechanisms of action and anatomical substrates for amphetamine induced psychosis are presented. Other topics included are: 1) the pharmacokinetics (metabolism) of amphetamines; 2) the roles of psychological stress, environmental conditions, differences in biological vulnerability, and other factors in the development of amphetamine induced or schizophrenic paranoia; 3) differences in the acute effects and chronic effects of amphetamine as related to its psychotic effects; and 4) the production of paranoid ideology and/or psychoses by other drugs such as lysergic acid diethylamide, cocaine, marijuana, various tricyclic antidepressants, L-DOPA, analgesics including opium alkaloids, and tranquilizers such as chlorpromazine and diazepam. It is proposed that at present the amphetamine psychosis appears most closely to fit the naturally occurring paranoid schizophrenic state; however, the problem of whether use of the drug in animal models are appropriate for a primarily cognitive disorder remains open to question. 78 references.

09 DRUG TRIALS IN AFFECTIVE DISORDERS

002414 Amin, M. M.; Ban, T. A.; Lehmann, H. E. Division of Psychopharmacology, Dept. of Psychiatry, McGill Univ., Montreal, Canada **Nomifensin in the treatment of depression: a report on the Canadian part of a transcultural study.** Psychopharmacology Bulletin. 14(1):35-37, 1978.

A paper read at a colloquium on clinical trials with antidepressants, organized by the Division of Psychopharmacology of McGill University and held at Pointe Claire, Quebec, June 1977, describing the Canadian part of a transcultural study of the effect of nomifensin in the treatment of depression is presented. A double-blind, standard controlled clinical trial was conducted to compare nomifensin with imipramine in the treatment of 20 depressed patients. There was statistically significant improvement in both groups (i.e. nomifensin and imipramine) on the total scores and the agitated depression, retarded depression, and anxiety/somatization factor scores of the Hamilton Psychiatric Rating Scale for Depression; on the total scores and the anxiety/depression, activation, and anergia factor scores of the Brief Psychiatric Rating Scale; and on the total scores and the mood disorders/emotional disturbances, psychomotor disorders, and disorders of drives and social behavior factor scores of the Psychopathological Assessment Scale of The Arbeitsgemeinschaft fur Methodik und Dokumentation in der Psychiatrie. The incidence of anticholinergic side-effects in the nomifensin group was about two thirds less than that in the imipramine group. 2 references. (Author abstract modified)

002415 Amin, M. M.; Ban, T. A.; Pecknold, J. C. Division of Psychopharmacology, Dept. of Psychiatry, McGill Univ., Montreal, Canada **Nomifensin in the treatment of depression: a standard-controlled clinical study.** Psychopharmacology Bulletin. 14(1):37-39, 1978.

A paper read at a colloquium on clinical trials with antidepressants, organized by the Division of Psychopharmacology of McGill University and held at Pointe Claire, Quebec, June 1977, describing a standard controlled clinical study of nomifensin in the treatment of depression is presented. A double-blind, standard controlled clinical trial was conducted to compare nomifensin with imipramine in the treatment of 30 depressed patients. While no statistically significant difference between the two drugs was found on the Clinical Global Impressions scale, more patients improved with imipramine than with nomifensin. On the other hand, the incidence of autonomic side-effects in the nomifensin group was about half of that in the imipramine group; but there was a tendency to greater weight loss in the nomifensin group. (Author abstract modified)

002416 Amin, M. M.; Ban, T. A.; Lehmann, H. E.; Marcotte, E. Division of Psychopharmacology, Dept. of Psychiatry, McGill Univ., Montreal, Canada **Doxepin and imipramine in the treatment of depression: a double-blind crossover clinical study with EKG recordings.** Psychopharmacology Bulletin. 14(1):39-42, 1978.

A paper read at a colloquium on clinical trials with antidepressants, organized by the Division of Psychopharmacology of McGill University and held at Pointe Claire, Quebec, June 1977, in which a double-blind crossover clinical study with EKG recordings of the treatment of depression with doxepin and imipramine is presented. In a 5 week, double-blind, crossover clinical trial with doxepin and imipramine in 20 patients with a diagnosis of depression, there was no statistically significant difference in the therapeutic effects of the drugs.

There was a statistically significant difference in the weight measures of the entire population in that they increased with doxepin administration. (Author abstract modified)

002417 Amin, M. M.; Cooper, R.; Khalid, R.; Lehmann, H. E. Division of Psychopharmacology, Dept. of Psychiatry, McGill Univ., Montreal, Canada **A comparison of desipramine and amitriptyline plasma levels and therapeutic response.** Psychopharmacology Bulletin. 14(1):45-46, 1978.

A paper read at a colloquium on clinical trials with antidepressants, organized by the Division of Psychopharmacology of McGill University and held at Pointe Claire, Quebec, June 1977, on a comparison of desipramine and amitriptyline plasma levels and therapeutic response in depressed patients is presented. In a 3 week, double-blind clinical study, no significant degree of relationship was found between improvement on total Hamilton Psychiatric Rating Scale for Depression (HAM-D) scores and the desipramine, amitriptyline, nortriptyline, as well as the amitriptyline and nortriptyline combined plasma levels. There was a positive correlation between improvement on the anxiety/somatization factor scores of the HAM-D and the amitriptyline, nortriptyline, as well as the amitriptyline and nortriptyline combined plasma levels. There was a negative correlation between improvement on the cognitive disturbance factor scores of the HAM-D and the amitriptyline, nortriptyline, and the combined amitriptyline and nortriptyline plasma levels. (Author abstract modified)

002418 Ananth, J.; Pecknold, J. C. Continuing Medical Education, Douglas Hospital, 6875 Lasalle Blvd., Verdun, P.Q., Canada **Prediction of lithium response in affective disorders.** Journal of Clinical Psychiatry. 39(2):95-100, 1978.

Means of identifying psychiatric patients with affective disorders who may respond to therapy with lithium carbonate are discussed with reference to clinical, biochemical, and familial genetic approaches to the problem. The important indicators of favorable lithium response include a definitive diagnosis of primary affective disorder, occurrence of less than four episodes of mania and depression within 1 year, psychotic features during both manic as well as depressive episodes, grandiose elated picture during manic episodes, a family history of bipolar illness, and response of affected family members to lithium treatment. While those with more than four episodes are not likely to respond to lithium therapy, those with episodes less frequent than once a year or two may not need prophylactic lithium. Among the depressed, hypersomnic depressed patients tend to respond to lithium combined with a monoamine oxidase inhibitor. In addition to clinical predictors of response to lithium treatment, there are a number of pharmacokinetic, neurophysiological and biochemical indices which have been employed as supplementary predictors of response to lithium therapy. 45 references. (Author abstract modified)

002419 Ananth, J.; Van Den Steen, Nancy. McGill University, Montreal, PQ, Canada **A double-blind controlled comparative study of nomifensine in depression.** Current Therapeutic Research. 23(2):213-221, 1978.

A double-blind comparative study of nomifensine, a new tricyclic antidepressant drug, and of amitriptyline conducted over a 6 week period in 30 depressed hospitalized patients is reported. Nomifensine was found to be as effective as amitriptyline in the treatment of depressed patients. However, nomifensine produced fewer side-effects compared with those of amitriptyline. Particularly, anticholinergic side-effects were virtually absent with nomifensine treatment. It is concluded that nomifensine is an effective and a safe antidepressant with some added advantage over the existing antidepressant drugs. 12 references. (Author abstract modified)

002420 Baastrup, P. C.; Christiansen, C.; Transbol, I. Kobenhavns Amts Sygehus Nordvang, DK-2600 Glostrup, Denmark **Calcium metabolism in lithium-treated patients: relation to uni-polar dichotomy.** Acta Psychiatrica Scandinavica (Kobenhavn). 57(2):124-128, 1978.

The bone mineral content (BMC) together with biochemical indices of calcium metabolism were measured in 83 manic-depressive patients on long-term lithium therapy. The patients were diagnosed and divided into a unipolar and a bipolar group according to strict symptomatic course criteria. The patients with bipolar course had a significantly decreased BMC, while the unipolar patients had normal BMC. Both groups had biochemical changes consistent with primary hyperparathyroidism. 18 references. (Author abstract)

002421 Baker, P. M.; Bartholemeusz, D. B.; Siskind, M.; Whitlock, F. A. Dept. of Psychiatry, Queensland 4029, Australia **Drug-induced depression and attempted suicide.** Medical Journal of Australia (Glebe). 2(10):322-324, 1977.

Drug induced depression and attempted suicide were studied to test the hypothesis that suicidal behavior might be a response to a mixture of medicaments taking by persons before making suicidal attempts. Sixty-eight patients who had attempted suicide were matched with nonsuicidal controls. It was found that: 1) suicidal patients were consuming more potentially depressing drugs; 2) far more of the suicide attempters had made previous suicide attempts than the controls; and 3) the potential hazard of treating schizophrenic suicidals with fluphenazine decanoate was confirmed. Two prophylatic measures are advised: 1) multiple prescribing of depot antipsychotics should be done after assessment of suicidal risk, and 2) when treating emotionally disturbed patients, the hazard of prescribing potentially depressing drugs to patients with past or present history of suicide attempt, depression, or alcoholism must be weighed.

002422 Broadhurst, A. D.; James, H. D.; Corte, L. Della; Heeley, A. F. Dept. of Psychiatry, West Suffolk Hospital, Bury St. Edmunds, Suffolk, England **Clomipramine plasma level and clinical response.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):139-145, 1977.

Clomipramine plasma level and clinical response was examined in 14 patients with endogenous depression treated with a fixed dose (150mg daily) of clomipramine. Plasma levels of the parent compound and its pharmacologically active metabolite desmethylclomipramine varied widely from patient to patient. A high degree of correlation was found between clomipramine dosage expressed as mg/kg bodyweight and the plasma concentration of desmethylclomipramine. Intermediate plasma levels of desmethylclomipramine were associated with the most marked antidepressive response, both higher and lower levels being associated with an inferior response. No relationship was found between plasma clomipramine levels and antidepressive effect. It is suggested that adjustment of clomipramine dosage to bring plasma desmethylclomipramine levels into the intermediate range may provide a means of helping some of the 35 to 40% of depressed patients apparently resistant to treatment with the drug. 18 references. (Author abstract modified)

002423 Burrows, Graham D.; Norman, Trevor R.; Maguire, Kay P.; Rubinstein, Gertrude; Scoggins, Bruce A.; Davies, Brian. Dept. of Psychiatry, Univ. of Melbourne, Melbourne,

Australia **A new antidepressant butriptyline: plasma levels and clinical response.** Medical Journal of Australia (Glebe). 2(18):604-606, 1977.

Plasma levels and clinical response were assessed in ten patients administered a new tricyclic antidepressant, butriptyline, for primary depressive illness. Six Ss showed marked clinical improvement, as judged by depression rating scores, at the end of 22 days. No simple relationship between clinical response and plasma butriptyline concentration was found. It is concluded that butriptyline is an effective antidepressant agent, well tolerated and with few side-effects. 21 references. (Author abstract modified)

002424 Checkley, S. A.; Crammer, J. L. Maudsley Hospital, Denmark Hill, London SE5, England **Hormone responses to methylamphetamine in depression: a new approach to the noradrenaline depletion hypothesis.** British Journal of Psychiatry (London). 131:582-586, 1977.

The corticosteroid and growth hormone responses to methylamphetamine in ten patients during depression and after recovery were investigated. The corticosteroid response to methylamphetamine was lower in ten patients when they were depressed than when they were recovered. The growth hormone responses to the same injection in the depressed and recovered states were not significantly different. This pattern of responses is seen in normal subjects after blockade of alpha-adrenergic receptors. A functional deficiency of noradrenaline at alpha-adrenergic receptors in these patients during the time they are depressed is suggested. 24 references. (Author abstract modified)

002425 Cole, Jonathan O.; Schatzberg, Alan F.; Frazier, Shervert H. Psychopharmacology Department, McLean Hospital, Belmont, MA **Depression: biology, psychodynamics, and treatment.** New York, Plenum Press, 1978. 250 p. $25.00.

The proceedings of a symposium on depression held in Belmont, Massachusetts, in March, 1976 are presented. Depressive disorders are examined from a variety of viewpoints including 1) biochemical (the amine hypothesis, the role of amine neurotransmitters and their metabolites in affective illness and drug response; 2) genetic; and 3) psychodynamic. Special emphasis is given to the treatment of depressive disorders including drug therapy, brief psychotherapy, hospital management, cognitive therapy and the interactions between drug therapy and psychotherapy. Classifications of depressive disorders using systems based fundamentally on symptoms and history and recent findings which suggest that differences in norepinephrine metabolism in patients with affective disorders may be useful biochemical criteria for distinguishing different types of depressions are discussed. A discussion of affective disorders in children and adolescents with special emphasis on depression is included.

002426 Coppen, A.; Ghose, K.; Montgomery, S.; Rama Rao, V. A.; Bailey, J.; Christiansen, J.; Mikkleson, P. L.; Van Praag, H. M.; Van de Poel, F.; Minsker, E. Medical Research Council Neuropsychiatry Laboratory, West Park Hospital, Epsom, Surrey, England **Amitriptyline plasma-concentration and clinical effect: a World Health Organization collaborative study.** Lancet (London). No.8055:63-66, 1978.

A World Health Organzation international collaborative study of the relationship between steady state plasma levels of amitriptyline (AT) and its active metabolite nortriptyline (NT), involving 54 patients at five international locations, is presented. Participants were in-patients with primary depression 16 or greater on the Hamilton Rating Scale for depression. No important correlations were found between steady state plasma levels of AT and therapeutic outcomes or corrected side-effects. Corrected side-effects correlated negatively with therapeutic outcome. It was concluded that routine monitoring of AT and NT seems pointless since plasma levels were found to be unrelated to variations in therapeutic outcome. 12 references. (Author abstract modified)

002427 Cwynar, Stanislaw; Soczynskia, Joanna; Szyburski, Marek; Wojdyslawska, Irena. Klinika Psychiatryczna AM, 159 Aleksandrowska ul., Lodz 91-229, Poland **/Clinical evaluation of trazodon./** Kliniczna ocena trazodonu. Psychiatria Polska (Warszawa). 11(3):313-317, 1977.

A study of trazodon used in 39 hospitalized patients and in 18 outpatients was presented. Results indicate that considerable improvement was obtained in 38 patients, i.e. in 66% of the sample examined. Patients with psychoneurosis and neurotic reaction showed remission of anxiety and improvement of mood. The effects obtained in depressive syndromes in the course of involution or an underlying organic condition and in cyclophrenia were improvement of mood and increased activity. The drug was well tolerated and produced only slight side-effects. It is suggested that trazodon can safely be used in outpatient treatment. (Journal abstract modified)

002428 Dell, A. J. no address **A comparison of maprotiline (Ludiomil) and amitriptyline (1).** Journal of International Medical Research (Northampton). 5(Supplement 4):22-24, 1977.

In a paper presented at a symposium on Ludiomil use in general practice, held at Torquay, England in June 1977, the action of maprotiline is compared with that of amitriptyline. The study described was designed specifically to see if it was possible to show an earlier onset of action for maprotiline (Ludiomil) compared with amitriptyline while at the same time demonstrating equal long term effectiveness and certainly no greater side effects. A between patient double-blind trial with 40 patients supported these aims and was statistically significant with regard to early onset of antidepressant effect. 2 references. (Author abstract modified)

002429 Donald, J. F. no address **A comparison of high and low dosage regimes of maprotiline (Ludiomil).** Journal of International Medical Research (Northampton). 5(Supplement 4):1-10, 1977.

In a paper presented at a symposium on Ludiomil in general practice held in Torquay, England, in June 1977, a double-blind, randomized, multicenter trial in depressed patients is described which was designed to compare the clinical effect of 30mg and 75mg daily of maprotiline (Ludiomil) administered as either once or thrice daily therapy. Physicians' assessment of patients' progress was made following 7, 14 and 28 days of treatment. Patients also assessed themselves using a visual analogue scale at the same time intervals. Of the 231 patients admitted to the study, 40 dropped out for various reasons, leaving 191 patients completing. Of the 40 dropouts, drug induced side-effects were considered to be responsible in the case of 17 patients. No differences between the four treatment groups were demonstrated on the physicians' assessment; however, the patients' self-assessments using the 10cm visual analogue scale indicated that the 25mg three times daily regime appeared to be the most satisfactory, but not statistically significantly so, when compared with the 10mg thrice daily and 75mg nocte regimes. The 30mg nocte dose proved to be distinctly inferior. 7 references. (Author abstract)

002430 Fabre, Louis F., Jr.; McLendon, David M. Fabre Clinic, 5503 Crawford Street, Houston, TX 77004 **Double-blind placebo-controlled study of bupropion hydrochloride (Wellbatrin) in the treatment of depressed in-patients.** Current Therapeutic Research. 23(3):393-402, 1978.

The first report of a double-blind, clinical trial of bupropion (n=23) vs. placebo (n=11), administered to hospitalized depressed patients for up to 4 weeks, is presented. The results show that relative to placebo, bupropion significantly decreased depressive symptomatology as measured by the Hamilton Depression Scale and Global Assessments at 3 and 4 weeks of treatment. There were no drug induced abnormalities in physical examinations, laboratory analyses, electrocardiograms and vital signs. No anticholinergic or other untoward side-effects were reported. The results indicate that bupropion is an effective antidepressant compound which appears to have minimal side-effects. 7 references. (Author abstract modified)

002431 Flemenbaum, Abraham; Weddige, Richard; Miller, John, Jr. Texas Tech University School of Medicine, Health Science Center, P.O. Box 4269, Lubbock, TX 79409 **Lithium erythrocycte/plasma ratio as a predictor of response.** American Journal of Psychiatry. 135(3):336-338, 1978.

The RBC/plasma lithium ratio was tested as a predictor of response to long-term followup treatment for depression. RBC/plasma lithium ratios were measured in 33 patients with primary diagnoses of unipolar depression (N equals 20), bipolar depression (N equals 9), schizoaffective psychosis (N equals 2), and alcoholism (N equals 2). Subjects rated as having marked or moderate improvement at followup (average equals 17.1months) tended to have high ratios, whereas all nine patients rated as minimally improved were in the low ratio group. Although further research with larger samples, controls, and longer followup is necessary, the results are seen to suggest a predictive value for the RBC/lithium ratio. 9 references. (Author abstract modified)

002432 Forrest, W. A. CIBA Laboratories, Horsham, West Sussex, England **Maprotiline (Ludiomil) in depression: a multicentre assessment of onset of action, efficacy and tolerability.** Journal of International Medical Research (Northampton). 5(Supplement 4):116-121, 1977.

In a paper presented at a symposium on Ludiomil in general practice held in Torquay, England, in June 1977, the onset of action, efficacy and tolerability of maprotiline (Ludiomil) are studied. The method used to detect unwanted effects indicates that maprotiline is well tolerated. The efficacy of once daily dosage, the good response in differing types of depressive illness, the early onset of effectiveness without serious side-effects in a wide age range of patients suggests that this drug will be a useful addition for the treatment of depressive illness in general practice. 5 references. (Author abstract modified)

002433 Forrest, W. A. CIBA Laboratories, Horsham, West Sussex, England **Maprotiline (Ludiomil) in depression: a report of a monitored release study in general practice.** Journal of International Medical Research (Northampton). 5(Supplement 4):112-115, 1977.

In a paper presented at a symposium on Ludiomil in general practice held in Torquay, England, in June 1977, a monitored release study of maprotiline (Ludiomil) is described. In a 3-week study of 10,000 general practice patients with depressive illness, a once nightly dose of 75mg maprotiline was effective therapy in three quarters of the patients who completed the study. At this dose the drug was well tolerated, and troublesome side-effects presented in only a small percentage of patients. Drowsiness was the most commonly reported side-effect, and the main reason for stopping treatment. The drug was acceptable to most physicians. and in this study was used in a wide age range of patients and over a broad spectrum of depressive illness. 7 references. (Author abstract)

002434 Gillis, John S. Oregon State University, Corvallis, OR **Selected combinations of amitriptyline and antipsychotic drugs and complex learning.** Current Therapeutic Research. 23(3):407-416, 1978.

The effects of combinations of psychoactive agents commonly used in the treatment of depression were evaluated on the ability of subjects to learn complex computer mediated tasks. Twenty-two hospitalized patients receiving such combinations were selected for inclusion on the basis of their present chemotherapeutic regimes. Patients were divided into two treatment groups: 1) one in which all subjects were receiving an amitriptyline/perphenazine combination; and 2) another in which patients were receiving amitriptyline plus an antipsychotic drug other than perphenazine. While none of the performance differences between the groups reached traditional levels of statistical significance, subjects in the amitriptyline/perphenazine group demonstrated generally superior awareness of task characteristics including subtle cue criterion relationships. 12 references. (Author abstract)

002435 Gold, Philip W.; Goodwin, Frederick K. Clinical Psychobiology Branch, National Institute of Mental Health, Bethesda, MD 20014 **Neuroendocrine responses to levodopa in affective illness.** Lancet (London). No. 8019:1007, 1977.

Significantly greater growth hormone increment and prolactin suppression following L-dopa therapy in bipolar depressed patients than in unipolar depressed patients or controls is discussed. Growth hormone response to L-dopa is partly related to the level of circulating estrogens, and is highest in premenopausal women, intermediate in men, and lowest in postmenopausal women. Analysis of growth hormone and prolactin responses to L-dopa in premenopausal women still shows a bipolar-unipolar difference. Some neurotransmitter metabolites in the cerebrospinal fluid differ significantly among males, premenopausal females, and postmenopausal females, further underscoring the need to consider sex and ovarian status in the analysis of neuroendocrine data from depressed patients. Other sources of variance are severity and phase of illness, stress, activity, time of day, and time of year. 7 references.

002436 Goldberg, I. J. L.; Lawton, K.; Ridges, A. P. Dept. of Chemical Pathology, Fazakerley Hospital, Liverpool, England **The effect of depression and its treatment on serum thyroxine.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):211-215, 1977.

To help clarify the effect of depression and its treatment on serum thyroxine, serum thyroxine levels were measured in depressed patients before, and after 7, 14 and 28 days' treatment with clomipramine or maprotiline, and in normal volunteers 24 hours after single 25mg and 50mg doses of clomipramine. In normal subjects no significant short-term effect of clomipramine was found, but in depressed patients, while neither clomipramine nor maprotiline produced any significant effect on serum thyroxine after 7 or 14 days, in every case of 28 days there was either an increase or a decrease, probably of sufficient magnitude to be considered significant. Although no consistent relationship emerged, high thyroxine

levels tended to fall and low levels to rise. This it is suggested, may be due to improvement in thyroid autoregulation when depression is successfully treated with clomipramine or maprotiline. 18 references. (Author abstract modified)

002437 Goldberg, Richard S.; Thornton, William E. Department of Psychiatry, Abraham Lincoln School of Medicine, University of Illinois, P.O. Box 6998, Chicago, IL 60680 **Combined tricyclic-MAOI therapy for refractory depression: a review, with guidelines for appropriate usage.** Journal of Clinical Pharmacology. 18(2-3):143-147, 1978.

A review of the literature on combined use of monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) in depressive patients who have proven refractory to treatment with electroconsulsive therapy, or MAOIs and TCAs alone is presented. Individual mechanisms of action of MAOIs and TCAs are discussed, and interactional theories for their combined effect are reviewed. In the 1960s, case reports of severe combined toxic reactions and deaths led to a moratorium on the combined use of these drugs. However, many of these cases were attributable to other than drug side-effects. A review of combined therapy reports failed to reveal any adverse reactions in several thousand patients. Guidelines for ensuring the safety of combined MAOI/TCA treatment are presented. It is concluded that the literature suggests that combined therapy, utilizing appropriate safeguards, can provide an effective treatment for refractory depression. 46 references.

002438 Halbreich, Uriel; Assael, Marcel; Ben-David, Menashe. Dept. of Psychiatry, Hadassah University Hospital, Jerusalem, Israel **Prolactin secretion during and after Noveril infusions to depressive patients.** Psychopharmacology (Berlin). 56(2):167-171, 1978.

A study was conducted to investigate prolactin secretion in depressed patients during and after high doses of dibenzapine (Noveril), a tricyclic antidepressant with strong noradrenergic and serotonergic actions. Dibenzapine (720mg) was infused intravenously to 16 depressed patients during a period of 3 hr. Serum prolactin levels were determined by radioimmunoassay and changes in clinical condition were evaluated according to the Hamilton Equation. In most of the patients dibenzapine caused a dramatic but short lived improvement in depressive symptoms. There was much variability in the prolactin response to the drug. Serum prolactin levels showed a great elevation in nine patients. In all patients the hormonal levels returned to their former normal levels after termination of the infusions. The treatment was then continued with dibenzapine per os. There was no significant correlation between serum prolactin levels and clinical condition or its change. The elevation of serum prolactin levels as a reaction to dibenzapine treatment may be explained by the prominent serotonergic action of dibenzapine. A time lag between serotonergic and dopaminergic actions of the drug when given in higher doses may be an additional explanation. 14 references. (Author abstract modified)

002439 Hofmann, G.; Rittmannsberger, H. Wagner-Jauregg-Krankenhaus, Linz, Austria **/Treatment of depressive syndrome with Noveril infusions./** Behandlung des depressiven Syndrome mit Noveril-infusionen. Wiener Medizinische Wochenschrift (Wien). 127(2):94, 1977.

The treatment of depression with dibenzepin (Noveril) is reported. Infusions of dibenzepin were given to 49 depressed women. The maximal dose was 720mg, and the infusion lasted 6 hr, continued for 5 to 10 days. Patients with inhibited endogenous depression responded best, showing 61.5% improvement, compared to 53% for the total group. Side-effects were frequent and strongly expressed on the first day of treatment, occurring in 60% of the patients. Elevated blood pressure and paroxysmal manifestations were particularly frequent. Significant improvement of mood occurred by the third or fourth day, and usual levels returned by the sixth or seventh day.

002440 Hullin, R. P. Department of Biochemistry, Univ. of Leeds, Leeds, England **Blood levels of tricyclic antidepressant drugs: assay procedures, reproducibility and relationship to therapeutic outcome and side effects.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):146-154, 1977.

The relationship between plasma levels of tricyclic antidepressants and clinical response is reviewed and it is suggested that the pattern may differ according to the drug given. On available evidence the relationship may be curvilinear for nortriptyline, and possible protriptyline, with optimal responses to an intermediate range of plasma levels and poorer responses above and below that range. A linear relationship seems more probable with amitriptyline and imipramine. Firm conclusions are hindered by inconsistencies between many of the findings reported. It is believed that the findings of studies being carried out to try and resolve these problems are helping clarify the picture, but further work will be required notably longitudinal studies of selected hospital patients, with careful control of drug dosage, blood sampling and other medication. 29 references. (Author abstract modified)

002441 Jobson, Kenneth; Burnett, Gordon; Linnoila, Markku. Clinical Psychopharmacology Clinic, University of North Carolina, North Carolina Memorial Hospital, Chapel Hill, NC 27514 **Weight loss and a concomitant change in plasma tricyclic levels.** American Journal of Psychiatry. 135(2):237-238, 1978.

A case history of a 33-year-old woman with a five-year history of unipolar depression who exhibited marked variation in her clinical response and her plasma drug levels to treatment with a tricyclic antidepressant, doxepin HCl, is discussed. The patient had a satisfactorily treated depressive state that relapsed with weight loss and cigarette smoking increase. It is suggested that this is an example of a therapeutic window effect. Additionally the patient's previously acceptable plasma drug level rose markedly while she was dieting, and the ratio of doxepin to desmethyldoxepin level shifted toward the desmethyl metabolite when she was on a calorie restricted diet. This rapid and substantial loss of adipose tissue may have induced an outpouring of desmethyldoxepin from the adipose tissue which was facilitated by changes in plasma pH and fatty acid concentration induced by fasting. Additional studies to elucidate the relationships between tricyclic levels and therapeutic efficacy are recommended. 6 references.

002442 Kerry, R. J.; Orme, J. E. Woodside Psychiatric Unit, Middlewood Hospital, Sheffield, England **Antidepressants -- yes or no?** British Medical Journal (London). No. 6101:1538, 1977.

The need to investigate the effectiveness of antidepressant drugs is discussed, and several drug studies are reviewed in the goal of determining patient subgroups for which antidepressant or electroconvulsive therapy is indicated. Results of an unpublished study which indicate that 98 depressed inpatients found no significant differences between amitriptyline, mianserin, and placebo in effectiveness, are disclosed. No subgroups who did well on antidepressants either on the Hamilton and Global clinical scales or on Cattell's clinical analysis questionnaire, were identified. 5 references.

002443 Khalid, R.; Amin, M. M.; Ban, T. A. Division of Psychopharmacology, Dept. of Psychiatry, McGill Univ., Montreal, Canada **Desipramine plasma levels and therapeutic response.** Psychopharmacology Bulletin. 14(1):43-44, 1978.

A paper read at a colloquium on clinical trials with antidepressants, organized by the Division of Psychopharmacology of McGill University and held at Pointe Claire, Quebec, June 1977, on desipramine plasma levels and therapeutic response in depressed patients is presented. In a 6 week, double-blind, crossover clinical study, desipramine administered in a single daily (morning) dose was found to be equal to desipramine administered in multiple (divided) daily doses. A statistically significant positive correlation was seen between plasma levels and improvement on Hamilton Psychiatric Rating Scale for Depression scores after 4 weeks of treatment. (Author abstract modified)

002444 Khvilivitskiy, T. Ya.; Mikhalenko, I. N.; Zlatkina, G. N. no address **/Use of lithium carbonate with retarded action (micalite) in patients with affective psychoses./** Primeneniye karbonata litiya prodlennogo deystviya -- mikalita -- u bol'nykh affektivnymi psikhozami. Zhurnal Nevropatologii i Psikhiatrii imeni S. S. Korsakova (Moskva). 77(4):583-587, 1977.

Micalite (microcapsulated lithium carbonate with retarded action) was used in the treatment of manic states and for prevention of attacks of manic depressive psychosis in 40 patients. The preparation was administered once daily. This provided the necessary concentration of lithium in the blood at a stable level. In regard to therapeutic effectiveness and frequency of side effects, micalite does not differ from other lithium preparations. However, a single daily administration of micalite produced significantly fewer disturbances in the treatment regime. 14 references. (Journal abstract modified)

002445 Kim, Yong B.; Dunner, David L.; Meltzer, Herbert L.; Fieve, Ronald R. Nassau County Medical Center, Hempstead, NY **Lithium erythrocyte:plasma ratio in primary affective disorder.** Comprehensive Psychiatry. 19(2):129-134, 1978.

The metabolism of the lithium ion, particularly the erythrocyte:plasma lithium ratio, in relation to clinical studies of affective disorder was investigated. Patients with primary affective disorder who have been chronically treated with lithium carbonate show a wide range of erythrocyte red blood cell (RBC)/plasma lithium ratios. The mean ratios for men and women or for the diagnostic subtypes do not reveal any significant differences, however. No correlations were found between ratios and age. Antidepressants and antipsychotic agents also have little effect on the ratio of RBC to plasma lithium. Data indicate that the RBC/plasma lithium ratio may not predict antidepressant response to lithium in acutely depressed patients, since most patients who have an antidepressant response to lithium are bipolar rather than unipolar. The mechanism of the RBC/plasma lithium ratio is discussed in terms of its wide range among individuals, its stability within individuals and its genetic control. During steady state conditions the RBC plasma lithium ratios may be determined by active transport processes which may in turn be under genetic control. 12 references.

002446 Lehmann, Erlo; Hopes, Helga. Rhein. Landeskrank. Duesseldorf, Psych. Universitaetsklinik, Bergische Landstr. 2, D-4000 Duesseldorf, Germany **Differential effects of a single dose of imipramine and lopramine in healthy subjects varying in their level of depression.** Progress in Neuro-Psychopharmacology (Oxford). 1(1/2):155-164, 1977.

The hypothesis that the antidepressant property of antidepressive agents can be demonstrated in experimental studies with healthy subjects was tested. Using 24 nonselected healthy male students, the effects of imipramine and lofepramine were compared with a placebo control on subjective, physiological, and performance variables. On the basis of their scores on the depression scale of the Freiburger Personality Inventory, the subjects were divided into two groups of 12 subjects each: high depressed and low depressed. Results of the subjective variables adjective check list and list of somatic symptoms indicate that imipramine and lofepramine elevated mood but only for the high depressed group. For the subjects scoring lower in depression no such effect was demonstrated. Also, fewer side-effects were reported for lofepramine than for imipramine. 15 references. (Author abstract modified)

002447 Lomas, D. M. no address **A comparative study of maprotiline (Ludiomil) and viloxazine in the management of depressed patients in general practice.** Journal of International Medical Research (Northampton). 5(Supplement 4):39-50, 1977.

In a paper presented at a symposium on Ludiomil in general practice held at Torquay, England, in June 1977, a double-blind, comparative, multicenter study comparing the efficacy and tolerability of maprotiline (Ludiomil) and viloxazine as antidepressants in general practice usage is described. Progress was measured at weekly intervals over the 4-week trial duration using a modified Hamilton Rating Scale and patient self-assessment visual analogue scales. A total of 127 patients were randomized into two groups, 63 patients being allocated maprotiline and 64 patients being allocated viloxazine. Of the patients receiving maprotiline, 12 withdrew during the course of the study compared to 9 patients receiving viloxazine. Maprotiline appeared to be superior to viloxazine on the sleep and sadness scales with some evidence to show it to be better also on the tension scale. Whilst the trend favored maprotiline, the two drugs did not appear to be significantly different on either the doctors' or the patients' assessments. There was little to choose between the drugs in terms of side-effects or ultimate patient tolerability and preference. 1 reference. (Author abstract)

002448 Luscombe, D. K.; Wright, Jayne; Jain, V. K. Welsh School of Pharmacy, UWIST, Cathays Park, Cardiff, Wales **Plasma level studies of clomipramine and desmethylclomipramine following intravenous infusions of clomipramine in depressive patients.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):88-96, 1977.

Plasma concentrations of clomipramine and desmethylclomipramine were quantitatively determined using a double radioisotope derivative technique in five outpatients who received daily intravenous infusions of clomipramine for management of depressive illness. Preinfusion levels of plasma clomipramine became relatively stable by the end of the treatment period, in the range of 30 to 50ng/ml, compared with concentrations of 130 to 150ng/ml on completion of infusions containing 150mg clomipramine. In contrast, plasma concentrations of the N-desmethyl metabolite were of the same order before and after each infusion and continued to rise throughout the treatment period. After the first day or two, foot point concentrations of desmethylclomipramine rose above the corresponding levels of the parent compound. In general, plasma foot point levels of both clomipramine and desmethylclomipramine were lower following intravenous infusions of 150mg clomipramine than previously observed in patients taking the same dose orally. 23 references. (Author abstract modified)

002449 Mahy, G. E. Black Rock Psychiatric Hospital, Delaware Medical Centre, Bridgetown, Barbados **Clinical effects and plasma levels of clomipramine in depressed Barbadians.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):87, 1977.

To determine if West Indian patients with depression may respond to rather lower doses of tricyclic antidepressants than those normally required elsewhere, a small pilot study was conducted in Black and White Barbadian patients with endogenous depression. Difficulties in ensuring continuity of therapy and/or correct dosage resulted in nearly half the patients failing to complete the study. But the clinical response in those who did so was better than usual, and plasma clomipramine levels were generally higher than those observed in other studies. Side-effects increased during the course of the study, at a time when they are usually found to fall. It is concluded that cultural influences appear to be responsible for unreliable drugtaking, while the high plasma levels can probably be attributed to environmental factors such as diet and climate. (Author abstract modified)

002450 McMillin, W. P. no address **A comparison of maprotiline (Ludiomil) and slow release amitriptyline (Tryptizol SR).** Journal of International Medical Research (Northampton). 5(Supplement 4):51-58, 1977.

In a paper presented at a symposium on Ludiomil in general practice held at Torquay, England, in June, 1977, a comparison of maprotiline (Ludiomil) and slow release amitriptyline (Tryptizol SR) is described. The subjects were 87 patients admitted to an open multicenter trial in the management of depression. Of these patients, 34 on Ludiomil and 34 on slow release amitriptyline finished the trial. There was no significant difference between the numbers or reasons for the dropouts for either drug. There was also no significant difference between the effects of both drugs or the side-effects, which largely comprised dry mouth and drowsiness. There was a greater proportional reduction in the loss of concentration, inability to cope and fatigue scores (especially in the first week) with Ludiomil than Tryptizol SR. Although statistically not significant, there was a very definite trend in favor of Ludiomil in regard to improvement in symptoms. There was an apparent three times greater improvement on the latter compared with Tryptizol SR treatment. This very definite trend cannot be without clinical significance in favor of Ludiomil. (Author abstract modified)

002451 Miller, P. I.; Beaumont, G.; Seldrup, J.; John, V.; Luscombe, D. K.; Jones, R. no address **Efficacy, side-effects, plasma and blood levels of maprotiline (Ludiomil).** Journal of International Medical Research (Northampton). 5(Supplement 4):101-111, 1977.

In a paper presented at a symposium on Ludiomil in general practice held at Torquay, England, in June of 1977, the antidepressant efficacy of Ludiomil in two studies conducted in general practice is discussed, with attention to plasma and blood levels of the drug and incidence of side-effects. In the first study depressed patients were given either 75mg of maprotiline in a single dose or 25mg three times daily. Assessments of the severity of depression and of side-effects were made initially and following 1, 2 and 4 weeks' treatment. At each assessment measurements of plasma levels of maprotiline were made. A second trial was performed in which some patients receiving 75mg single dose of maprotiline had whole blood levels of maprotiline assayed. Steady state levels of maprotiline were achieved after 1 week, but these levels showed considerable individual variability. No clear correlation emerged between clinical response, side-effects and plasma or blood levels. Some of the factors which may be responsible are discussed. 1 reference. (Author abstract modified)

002452 Mindham, B. A. E. no address **A comparison of maprotiline (Ludiomil) with amitriptyline (2).** Journal of International Medical Research (Northampton). 5(Supplement 4):25-33, 1977.

In a paper presented at a symposium on Ludiomil in general practice held at Torquay, England, in June 1977, the antidepressant effects of maprotiline and amitriptyline are compared. Seventy five patients were admitted to a double-blind multicenter trial of maprotiline (Ludiomil) and amitriptyline in the management of depression in general practice. Forty-seven patients, twenty-one on maprotiline and twenty-six on amitriptyline completed the study. Statistical analysis of admission data showed that the groups were not strictly comparable in that the maprotiline group contained many more males and had a greater average age. Nevertheless, although there was a suggestion that amitriptyline was faster acting in the younger age group that received it, there were no statistically significant differences between the two treatment groups as regards onset of effect, clinical efficacy or tolerability. (Author abstract)

002453 Mulgirigama, L. D.; Pare, C. M. B.; Turner, P.; Wadsworth, J.; Witts, D. J. Dept. of Psychological Medicine, St. Bartholomew's Hospital, London, England **Clinical response in depressed patients in relation to plasma levels of tricyclic antidepressants and tyramine pressor response.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):155-159, 1977.

Clinical response in depressed patients is examined in relation to plasma levels of tricyclic antidepressants and tyramine pressor response. Twenty-eight patients with endogenous depression and 22 with neurotic/reactive depression were allocated at random to treatment with maprotiline or clomipramine given double-blind. Patients with endogenous depression benefited far more from either drug than did those with neurotic/reactive depression, but no evidence was found that a clinically different type of patient responded to one drug rather than the other. At the dosages used, clomipramine was more effective than maprotiline in endogenous depression, 80% and 54% of patients respectively achieving complete remission by the fifth week. No correlation between plasma drug concentration and therapeutic response was found, but clomipramine exerted a markedly greater effect on the tyramine pressor response. 6 references. (Author abstract modified)

002454 Murphy, J. Eric. no address **A comparison of Ludiomil, Tryptizol, and Lentizol.** Journal of International Medical Research (Northampton). 5(Supplement 4):34-38, 1977.

In a paper presented at a symposium on Ludiomil in general practice held at Torquay, England, in June, 1977, the clinical efficiency and tolerability of maprotiline (Ludiomil), and two forms of amitriptyline (Tryptizol and Lentizol) were compared. The subjects were 176 patients admitted to an open, multicenter, comparative trial of Ludiomil, Tryptizol SR and Lentizol, each administered in a dose of 75mg at night: 57 patients received Tryptizol SR, 60 received Lentizol and 59 received Ludiomil. Nine patients on Tryptizol SR, ten patients on Lentizol and six patients on Ludiomil dropped out for a variety of reasons. A seventeen symptom rating scale was used and the symptoms analyzed individually. A greater response in the severity and number of symptoms was seen in the first week

of treatment on Ludiomil though the differences rarely reached the acceptable level of statistical significance. Global assessments did not reveal any differences between the groups. Side-effects were also similar. Only dry mouth and drowsiness were persistent problems. (Author abstract)

002455 no author. no address **Choosing an antidepressant.** British Medical Journal (London). No. 6106:128, 1978.

The range of available antidepressant drugs is surveyed to aid clinicians in determining the drugs of choice. Although many new drugs claim novel structure, the relation of activity to structure is not clear. Other criteria, particularly dosage scheduling, unwanted and toxic effects (of tricyclic antidepressants) and cardiotoxicity should be considered. It is recommended that generally secondary psychotropic actions (sedative and stimulant effects) be determining factors in prescription choice. 7 references.

002456 Pecknold, J. C.; Van den Steen, Nancy; Ananth, J.; Krishnappa, U. St. Mary's Hospital, 3830 Lacombe Avenue, Montreal, Quebec H3T 1M5, Canada **Trimipramine in the treatment of anxious-depressed out-patients.** Current Therapeutic Research. 23(1):94-100, 1978.

To examine the clinical effectiveness of trimipramine, 30 anxious/depressed outpatients were administered trimipramine in daily dosages ranging between 75mg and 200mg. Trimipramine was found to be an effective antidepressant agent similar to other tricyclic antidepressant medications. Test scores indicated that the medication produced statistically significant improvement on most of the items except the items of depersonalization, paranoid symptoms, and obsessive compulsive symptoms at the end of 3 weeks. In addition, this drug was found to be effective in relieving anxiety in anxious depressed patients. The improvement of anxiety was statistically significant at the end of the first week of the study. It is concluded that trimipramine is an effective and a safe antidepressant, and in addition to its antidepressant potential, the drug also has anxiolytic properties. 2 references. (Author abstract modified)

002457 Pishkin, Vladimir; Fishkin, Steven M.; Shurley, Jay T.; Lawrence, Betsy E.; Lovallo, William R. VA Hospital, 151A, 921 N.E. 13th St., Oklahoma City, OK 73104 **Cognitive and psychophysiologic response to doxepin and chlordiazepoxide.** Comprehensive Psychiatry. 19(2):171-178, 1978.

A total of 72 patients participated in a double-blind evaluation of chlordiazepoxide and doxepin to assess the drugs' antianxiety, antidepressant, cognitive, and psychophysiologic effects. To examine cognitive performance, Ss were exposed to success or failure on a prior task and were given high or low levels of motivation on a final concept identification task. Levels of anxiety and depression were assessed pre/posttreatment. Galvanic skin response (GSR), EMG, and heartrate were also evaluated. For depressed Ss, high depression was associated with low autonomic arousal and low depression with high arousal while for controls the reverse was true. Doxepin patients improved to a greater extent than chlordiazepoxide patients, particularly on measures of depression. Autonomic activity was higher in the success than the failure patients with low motivation; opposite effect was shown with high motivation. Results suggest that cognitive functioning of patients on typical doses of doxepin or chlordiazepoxide for a 2 week period did not differ from controls; it is further suggested that doxepin may mitigate the effect of antecedent failure. 14 references.

002458 Price, John; Ward, Glenn. Department of Psychiatry, Clinical Sciences Building, Royal Brisbane Hospital, Brisbane, Queensland 4029, Australia **Cyproheptadine in bipolar affective illness with Cushingoid features.** Australian and New Zealand Journal of Psychiatry (Carlton). 11(3):201-202, 1977.

A case of bipolar affective illness with Cushingoid features which was treated with cyproheptadine is reported. The patient, aged 34, developed depressive illness 3 months after the birth of her seventh child and did not respond to several courses of treatment over a two-year period. Eighteen months following childbirth features suggestive of Cushing's disease developed: hirsutes, 16kg weight gain, easy bruising, plethoric facies and mauve abdominal striae. Excreted urinary free cortisol was excessive. It is reported that administration of a cyproheptadine/tricyclic antidepressant combination controlled depressive symptoms, and established normal urinary free cortisol to creatinine ratios; thus far, the only Cushingoid features that have changed are those of bruising and mauve abdominal striae. 7 references.

002459 Raskin, Allen; Boothe, Helvi; Reatig, Natalie; Schulterbrandt, Joy G. Psychopharmacology Research Branch, NIMH, 5600 Fishers Lane, Room 9-101, Rockville, MD 20857 **Initial response to drugs in depressive illness and psychiatric and community adjustment a year later.** Psychological Medicine (London). 8(1):71-79, 1978.

A study designed to determine whether treatment for acute depression with imipramine is more enduring and less likely to result in new depressive episodes than treatment with either chlorpromazine or a placebo and whether an initial response to any or all of these three treatments is related to psychiatric and social adjustment at one year is reported. Subjects for the study were 360 depressed inpatients initially treated with imipramine, chlorpromazine, or a placebo and reevaluated one year later. Results showed that the depressed patients showing the poorest community adjustment at one year were those who failed to show a good initial response to drug treatment and those who responded positively to a placebo. It is concluded that more work needs to be done not only in identifying additional factors which characterize depressed patients with poor long-term community adjustment but in assessing the prophylactic benefits to these patients of various drug and/or psychotherapeutic approaches. 18 references.

002460 Reisby, Niels; Gram, Lars F.; Bech, Per; Nagy, Adam; Petersen, G. O. Dept. of Psychiatry, Kommunehospitalet, DK-1399 Copenhagen K, Denmark **Imipramine: clinical effects and pharmacokinetic variability.** Psychopharmacology (Berlin). 54(3):263-272, 1977.

In a study of the clinical effects and pharmacokinetic variability of imipramine, 66 hospitalized depressed patients were treated for 4 weeks with imipramine (Tofranil), blood samples were drawn twice weekly 15 h after the last drug intake, and IP and DMI concentrations in plasma were assayed by quantitative in situ thin layer chromatography. Clinical rating was carried out once weekly by Hamilton's Rating Scale (HRS), Beck's Depression Inventory, WHO Depression Scale (Quantitative Part), and a side-effect scale. The patients were classified on the basis of the WHO Depression Scale (Qualitative Part) as "endogenous" (N=37) or "nonendogenous" depressions (N=29). Antidepressive effect was evaluated on the basis of the posttreatment rating scores. In patients classified as endogenous depressives all 12 responding patients had plasma levels of IP higher than 11 out of 14 nonresponding patients. There was no sign of an upper plasma level limit for the antidepressive effect of imipramine.

The plasma level/effect relationship was less clear in patients with nonendogenous depressions, since several of them responded at low plasma levels. Some relationship between effect on blood pressure (orthostatic effect) and high plasma levels of IP and DMI was found. Using a plasma level limit, it was possible to predict the response of the endogenous depression group for 10 out of 12 responders and 10 out of 14 nonresponders on the basis of plasma level measurements obtained after 1 week of treatment. 28 references. (Author abstract modified)

002461 Ruger, Ulrich. Psychiatrische Klinik der Freien Universitat Berlin, Nussbaumallee 36, D-1000 Berlin 19, Germany **/Intrapsychic and family dynamic processes in an endogenous depression preceding manifestation of the illness and lithium therapy./** Intrapsychische und familiendynamische Prozesse vor der manifesten Erkrankung und wahrend der Lithium-Therapie einer endogenen Depression. Zeitschrift fur Psychosomatische Medizin und Psychoanalyse (Gottingen). 23(4):329-350, 1977.

The familial and intrapsychic circumstances surrounding the manic-depressive syndrome of a female patient who had been treated for 7 years with lithium after a number of depressive and manic phases were examined to assess lithium therapy effects. A detailed profile of the patient's family relationships and her background was based on a psychological interview with the patient and all members of her family, as well as on psychological tests (Freiburg Personality Inventory and Giessen Test). Lithium therapy was shown to have effectively stabilized the condition of the patient by reducing the capacity for perception in general and thereby shielding against the appearance of very early, strongly ambivalent fantasies which correspond to external conflict situations. While the range of human experience was limited during this period, lithium treatment enabled the patient to deal without fear with previously shattering conflict situations. 29 references. (Author abstract modified)

002462 Scharbach, H. Service Psychiatrie, C.H.R., Nantes, France **/Beta-blocking substances in psychiatric chemotherapy./** Les substances beta-bloquantes en chimiotherapie psychiatrique. Revue de Neuropsychiatrie de l'Ouest (Rennes). 14(55):3-29, 31-34, 1977.

The action of the beta-blocking agents alprenolol and oxprenolol, their neurophysiological bases, and psychiatric chemotherapeutic effectiveness were examined in a clinical study with 47 psychiatric patients. An axiolytic effect was observed in both neurotic and psychotic patients. Thymoanaleptic effect was noted, stimulating in some patients, and normalizing states of excitation in others. The antimanic action indicates a type of normothymic effect. Effect of vigilance showed an improvement in attention in hypoprosexic patients and an increase in interest in surroundings. Autoaggressive and heteroaggressive manifestations were reduced, but with paradoxic phenomena and rebound during the weeks following termination of administration. No significant antidelusional or antihallucinatory effect was recorded. At the dosage used, tolerance was good in 15 cases, and benign toxic effects were observed in most others. 71 references.

002463 Shaw, D. M.; Francis, A. F.; Groom, G. V.; Riad-Fahmy, D. Biochemical Psychiatry Laboratory, Whitchurch Hospital, Cardiff, Wales **A pilot endocrine study in depression.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):172-174, 1977.

A pilot study of pituitary and pituitary controlled hormone concentrations was carried out in three groups of depressed patients. No significant changes in the levels of luteinizing hormone, follicle stimulating hormone, growth hormone, thyroid stimulating hormone, estradiol, progesterone or testosterone were revealed. Prolactin levels were high in three patients receiving treatment (two with neuroleptics, one with tranylcypromine) but within normal limits in the remainder. Cortisol levels tended to be high and to fall with recovery but no consistent pattern was identified. 9 references. (Author abstract modified)

002464 Shopsin, Baron. NYU School of Medicine, Unit for the Study & Treatment of the Affective Disorders, 550 First Ave., New York, NY 10016 **Enhancement of the antidepressant response to L-tryptophan by a liver pyrrolase inhibitor: a rational treatment approach.** Neuropsychobiology (Basel). 4(3):188-192, 1978.

The effect of precomitant and concomitant treatment with a liver pyrrolase inhibitor, allopurinol, on depressed male outpatients receiving L-tryptophan was investigated. Results indicate that patients (n=8) concomitantly treated with tryptophan plus the pyrrolase inhibitor showed a significant improvement in Hamilton Depression ratings at treatment termination. Side-effects from allopurinol included mild and transient drowsiness (1 patient), nausea (2 patients), and diarrhea and soft stools (1 patient). It would appear that serotonin, or rather an excess in serotonin, is involved in the symptomatic relief of depressions in man. 16 references.

002465 Smith, R.; Amin, M. M.; Ban, T. A. Reddy Memorial Hospital, Montreal, Canada **Trimipramine in the treatment of depression: a comparison of single vs. divided dose administration.** Psychopharmacology Bulletin. 14(1):42-43, 1978.

A paper read at a colloquium on clinical trials with antidepressants, organized by the Division of Psychopharmacology of McGill University and held at Pointe Claire, Quebec, June 1977, on a comparison of single vs. divided dose administration of trimipramine in the treatment of depression is presented. A 6 week clinical study was conducted to compare the efficacy of a single bedtime dose of trimipramine with that of divided doses of the drug in the treatment of 30 depressed psychiatric outpatients. Statistically significant improvement occurred in the entire population on the total scores and all five factor scores of the Hamilton Psychiatric Rating Scale for Depression and on the total scores and anxiety/depression, anergia, activation, and hostility/suspiciousness factor scores of the Brief Psychiatric Rating Scale. The single dose group, with a lower mean daily trimipramine dosage at the end of drug administration, tended to show greater overall improvement than the divided dose group. The most frequently occurring adverse effects in the single dose group were drowsiness and dry mouth, while the most frequently occurring adverse effects in the divided dose group were drowsiness and syncope/dizziness. These findings show that a single bedtime dose of trimipramine is equal and may be superior in its therapeutic efficacy to divided doses of the drug in the treatment of depression. (Author abstract modified)

002466 Sulser, Fridolin; Vetulani, Jerzy; Mobley, Philip L. Department of Pharmacology, Vanderbilt Univ. School of Medicine, Nashville, TN 37217 **Mode of action of antidepressant drugs.** Biochemical Pharmacology (Oxford). 27(3):257-261, 1978.

The mechanism of action of antidepressant drugs in humans was investigated in various experimental studies. The current

catecholamine and/or idolealkylamine hypothesis is favored in studies showing the relationship between blockade of reuptake of catecholamines and/or indolealkylamines and relief or reversal or depressive symptomatology. But some drugs have been found effective at dosages that did not influence the reuptake of amines, although interaction with noradrenergic or serotonergic mechanisms was not ruled out. Moreover, chronic administration of antidepressant drugs produces results varying from acute effects, indicating changes in the biosynthetic capacity. Other mechanisms for action have been suggested as monoamine oxidase inhibition and increased availability of norepinephrine and/or serotonin at postsynaptic receptor sites. A cyclic AMP generating system in the limbic forebrain is suggested as the site of affect. Emerging hypotheses of antidepressant drug mechanisms emphasize postsynaptic receptor mediation. 76 references.

002467 Waxman, David. Dept. of Psychological Medicine, Central Middlesex Hospital, London, England **The treatment of depression comparing divided and single doses of maprotiline (Ludiomil).** Journal of International Medical Research (Northampton). 5(Supplement 4):11-21, 1977.

In a paper presented at a symposium on Ludiomil in general practice held at Torquay, England, in June of 1977, a clinical trial of 75 patients suffering from depressive illness and treated with maprotiline (Ludiomil) is reported. Twenty-eight patients were given a single nightly dose of 75mg and twenty-six patients were treated with 25mg three times daily. Twenty-one patients withdrew from the trial. It was found that those patients on the nocte regime made greater improvement than those on the divided dosage. Sleep disturbances and mood swings were significantly improved on the nocte dosage. Both regimes were equally well tolerated. Special care was taken in recording any adverse drug effects in order to distinguish these from preexisting symptoms of the illness. 7 references. (Author abstract)

002468 Wehr, Thomas; Goodwin, Frederick K. Clinical Psychobiology Branch, National Institute of Mental Health, 9000 Rockville Pike, Bethesda, MD 20014 **Tricyclic antidepressants accelerate manic-depressive cycles. (Unpublished paper).** Bethesda, MD, NIMH, 1977. 19 p.

The effect that tricyclic antidepressants have on manic-depressive cycles was investigated. In five female manic-depressive patients studied longitudinally, mood cycle frequency was markedly accelerated by tricyclic antidepressant drugs from one cycle every 2 to 8 months to one cycle every 1 to 6 weeks. In a sixth patient a similar effect was observed with a monoamine oxidase inhibitor. It is concluded that antidepressent drugs should be more broadly conceived as accelerating the entire cyclic illness process rather than counteracting only one of its phases and therefore their effect on the spontaneous frequencies of other rhythmic biological processes should be explored. 14 references. (Author abstract modified)

002469 Witts, D. J.; Mulgirigama, D.; Turner, P.; Pare, C. M. B. Dept. of Clinical Pharmacology, St. Bartholomew's Hospital, London, England **Some observations on patient compliance in an antidepressive trial.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):136-138, 1977.

Some observations on patient compliance in an antidepressive trial are presented. Estimations of plasma drug levels during a clinical trial of clomipramine and maprotiline can indicate that the patient is taking the medication regularly as directed, having reached a steady state level as defined, or that the patient is probably not taking the drug prescribed as it is not detectable in the plasma. It is also possible to determine if the patient is probably receiving the wrong drug, as it is present in expected plasma concentration and/or the patient is taking the correct drug but erratically and not as prescribed, because large variations in plasma level are found. A final possibility was concluded in which the patient is taking instead of, or in addition to, his antidepressive drug, another medication such as a benzodiazepine which is detected in the plasma, and which may influence the therapeutic or toxic effects of the drug under investigation. 3 references.

002470 Wright, Jesse H.; Denber, Herman C. B. Dept. of Psychiatry, School of Medicine, University of Louisville, Louisville, KY **Clinical trial of fluvoxamine: a new serotonergic antidepressant.** Current Therapeutic Research. 23(1):83-89, 1978.

To evaluate the clinical efficacy and possible side-effects of fluvoxamine, a new serotonergic antidepressant, 12 hospitalized patients were treated with fluvoxamine in an initial clinical trial. There was significant improvement after 2 and 4 weeks of treatment as measured by the Hamilton, Zung, and Beck depression rating scales. Ten of the twelve patients showed moderate or marked improvement on the Clinical Global Impression Scale. In most patients, fluvoxamine was tolerated well with minimal or no side-effects. The high response rate of depressed patients to fluvoxamine suggests antidepressant activity which awaits verification from further study. 10 references. (Author abstract modified)

002471 Youngerman, Joseph; Canino, Ian A. Bronx Children's Psychiatric Center, 1000 Waters Place, Bronx, NY 10461 **Lithium carbonate use in children and adolescents: a survey of the literature.** Archives of General Psychiatry. 35(2):216-224, 1978.

To help develop guidelines for the use of lithium carbonate in the treatment of depression and other psychiatric conditions in children, 190 cases of lithium carbonate use in children and adolescents were reviewed and divided according to DSM II criteria into major affective disorders, behavior disorders of childhood and adolescence and schizophrenia, childhood type. In a group of well described cases of 25 males and 21 females, aged 3 to 19, there were 30 positive responses to lithium carbonate. The affective component, irrespective of diagnosis, in youngsters responding to lithium carbonate is claimed as impressive. The many incompletely reported cases prevent conclusive generalization and illustrate the need for well documented studies correlating clinical, familial, and biochemical indices. 37 references. (Author abstract modified)

002472 Ziegler, Vincent E.; Biggs, John T. Department of Psychiatry, Washington University School of Medicine, 4940 Audubon Ave., St. Louis, MO 63110 **Tricyclic plasma levels: effect of age, race, sex, and smoking.** Journal of the American Medical Association. 238(20):2167-2169, 1977.

Steady state plasma tricyclic antidepressant levels were determined in 65 patients undergoing treatment for depression with either amitriptyline hydrochloride or nortriptyline hydrochloride to determine if common factors such as age, race, sex, or smoking status were predictors of steady state drug levels that have been shown to vary up to 36 fold. Evaluation of these factors did not disclose differences in the rate of demethylation of amitriptyline to nortriptyline, or steady state tricyclic levels in the amitriptyline treated patients. No differences were found in the nortriptyline treated patients except regarding race. Black patients had significantly higher (50%) nortriptyline plasma levels than did White pa-

tients, which may explain the more rapid response to tricyclic treatment demonstrated in Blacks. Decreased rates of nortriptyline metabolism in Blacks can result in increased side-effects and treatment failure if the therapeutic plasma range is exceeded. 10 references. (Author abstract)

10 DRUG TRIALS IN NEUROSES

002473 Amin, M. M.; Ban, T. A.; Pecknold, J. C.; Klingner, A. Division of Psychopharmacology, Dept. of Psychiatry, McGill University, Montreal, Canada **Clomipramine (Anafranil) and behaviour therapy in obsessive-compulsive and phobic disorders.** Journal of International Medical Research (Northampton). 5(Supplement 5):33-37, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive neuroses and phobic disorders in Montreal, May 1977, a comparative study of three treatment regimes in patients with obsessive-compulsive or phobic manifestations is presented. The most favorable therapeutic findings were seen in the clomipramine (Anafranil) plus behavior therapy group and the least favorable therapeutic findings in the clomipramine plus simulated behavior therapy group. The findings that a combination of behavior therapy and clomipramine results in more favorable therapeutic changes than either of the two treatments alone are in line with reported studies in the literature. 19 references. (Author abstract modified)

002474 Ananth, J. Continuing Medical Education, Douglas Hospital, Montreal, Quebec, Canada **Treatment of obsessive-compulsive neurosis with clomipramine (Anafranil).** Journal of International Medical Research (Northampton). 5(Supplement 5):38-41, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive neuroses and phobic disorders in Montreal, May 1977, an uncontrolled clinical study to evaluate the therapeutic efficacy of clomipramine (Anafranil), in a group of 20 obsessive-compulsive neurotic patients is reported. Clomipramine proved to be extremely useful in alleviating obsessive-compulsive neurosis as well as phobia. This finding was not secondary to the improvement in anxiety or depression which occurred, as the degree of improvement in obsessive symptoms far exceeded the improvement in the other symptoms. 14 references. (Author abstract)

002475 Beaumont, G. Neuropsychiatric Research Group, Research & Medical Dept., CIBA-GEIGY (UK) Ltd., Macclesfield, Cheshire, England **A large open multicentre trial of clomipramine (Anafranil) in the management of phobic disorders.** Journal of International Medical Research (Northampton). 5(Supplement 5):116-123, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive neuroses and phobic disorders in Montreal, May 1977, a large, open multicenter trial of clomipramine in the management of phobic disorders is described. The subjects were 765 patients suffering from agoraphobia or social phobias, of whom 480 completed a 12 week course of treatment. Of 285 withdrawals, 139 were due to side-effects. Good results were obtained on all measures of phobias in those patients who completed the study, with improvements being of the order of 70 to 80%, and over 50% of patients being symptom free. (Author abstract modified)

002476 Burrows, Graham D.; Dumovic, Peter; Smith, Judith A.; Norman, Trevor; Maguire, Kay. Department of Psychiatry, Clinical Sciences Building, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia **A controlled comparative trial of clorazepate (Tranxene) and diazepam (Valium) for anxiety.** Medical Journal of Australia (Glebe). 2(16):525,527-528, 1977.

In order to compare the efficacy of clorazepate (Tranxene) and diazepam (Valium) and their antianxiety properties, two groups of anxious patients were treated with either clorazepate (once at night) or diazepam (three times a day) during a 22 day period. Both drugs were effective antianxiety agents as assessed by the Hamilton Anxiety Scale and the Analogue and Rapid Symptom Check List. The response to drug treatment did not differ according to the type of anxiety, psychological or somatic. No significant difference was observed between the two drug treatments and separation of patients according to their anxiety type did not change this finding. It is concluded that clorazepate, when administered as a single dose at night, is an effective short-term anxiolytic. 18 references. (Author abstract modified)

002477 Capstick, Norman. Graylingwell Hospital, Chichester, West Sussex, England **Clinical experience in the treatment of obsessional states (1).** Journal of International Scientific Research (Northampton). 5(Supplement 5):71-80, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive neuroses and phobic disorders in Montreal, May 1977, the treatment with clomipramine of 33 patients suffering obsessional symptoms is described. The symptoms were classified into phobic ruminations, nonphobic ruminations, and rituals as well as into the less familiar group of normal and bizarre obsessions. The results show that clomipramine possesses a specific antiobsessional quality and that the use of this preparation is an effective treatment for obsessional patients. Certain aspects of therapy as well as an etiological basis of obsessional symptoms are discussed. 4 references. (Author abstract modified)

002478 Ellison, Roy J., Jr.; Cancellaro, Louis A. Comprehensive Community Mental Health Center, Pickens Hospital, Greenville, SC 29605 **A study of the management of anxiety with lorazepam.** Journal of Clinical Pharmacology. 18(4):210-219, 1978.

To examine clinical efficacy and side-effects, a four week double-blind comparison of lorazepam and placebo was undertaken in 60 anxiety patients. Results revealed that lorazepam in a mean dose of approximately 3mg on a b.i.d. regimen is significantly and clinically more effective than placebo for almost all items of the Global, Hamilton, and 35-Item scales at nearly all evaluation periods. Moreover, lorazepam was associated with a 50% greater improvement rate than was placebo. Except for only one patient who was withdrawn from the study because of severe sedation, lorazepam was well tolerated and did not interact adversely with concomitant nonpsychoactive medication. 17 references. (Author abstract modified)

002479 Fabre, Louis F., Jr.; McLendon, David M.; Reynolds, John W.; Hornyak, E. Paul. Fabre Clinic, 5503 Crawford Street, Houston, TX 77004 **Pilot open label study of brofoxine in anxiety.** Current Therapeutic Research. 23(1):105-110, 1978.

To examine the clinical efficacy of brofoxine, a novel compound with anxiolytic activity but without sedative or skeletal muscle relaxant properties, 17 outpatients with anxiety neurosis of moderate intensity as measured by the Hamilton Anxiety Scale, were treated with brofoxine in an uncontrolled study. Anxiety symptoms were considerably ameliorated at 7

days, and improvement persisted throughout the 21 day study period. The average dose ranged from 60 to 150mg per day. Side-effects were minimal. No consistent laboratory evaluation abnormality could be attributed to brofoxine. 1 reference. (Author abstract modified)

002480 Friedman, Stanley; Kantor, Irwin; Sobel, Stuart; Miller, Robert. Department of Psychiatry and Dermatology, Mount Sinai School of Medicine, Ann. 22-44, 11 East 100th Street, New York, NY 10029 **On the treatment of neurodermatitis with a monoamine oxidase inhibitor: the chemotherapy of psychosomatic illness through A-REM suppression.** Journal of Nervous and Mental Disease. 166(2):117-125, 1978.

Treatment of the psychosomatic disease neurodermatis with a monoamine oxidase inhibitor was conducted to test the hypothesis that suppression of the rapid eye movement (REM) phase of the sleep/dream cycle would lead to improvement of psychosomatic disorders. Phenelzine sulfate was used to suppress REM and diazepam was the control drug used. Fifteen randomly assigned subjects (control and experimental) had a 5 week introductory period during which time they all received a dose of phenelzine sulfate too small to block the REM state, followed by a 5 week double-blind study. The essential hypotheses were that subjects should not improve during the 5 experimental weeks, and that experimental subjects should improve significantly during the experimental weeks. Of the 24 predictions 23 were supported by the results. The degree of statistical significance was especially great in the primary symptoms of pruritus, erythema, and papules where structural change was less and reversibility was more rapid. It is noted that the significant findings do not comprise a crucial experiment since alternate models can account for the results. 21 references. (Author abstract modified)

002481 Gringras, M. no address **An uncontrolled trial of clomipramine (Anafranil) in the treatment of phobic and obsessional states in general practice.** Journal of International Medical Research (Northampton). 5(Supplement 5)):111-115, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive neuroses and phobic disorders in Montreal, May 1977, a multicenter open trial of clomipramine in general practice is discussed in which new rating devices were used. Twenty seven patients suffering from a variety of phobias and obsessions were treated with doses of clomipramine up to a maximum of 225mg daily for 6 weeks. In phobic subjects best results were obtained in social phobias, agoraphobia and diffuse phobic anxiety; there was response in all situational anxiety, interference, avoidance, and autonomic effects. An improvement of between 33% and 47% was seen in obsessional symptoms. 2 references. (Author abstract modified)

002482 Haskell, D. S.; Gambill, J. D.; Gardos, G.; McNair, D. M.; Fisher, S. Westwood Lodge, Westwood, MA **Doxepin or diazepam for anxious and anxious-depressed outpatients?** Journal of Clinical Psychiatry. 39(2):135-139, 1978.

The comparative efficacy of doxepin and diazepam in the treatment of anxious and anxious/depressed patients is examined. A 6 week double-blind comparison of doxepin and diazepam in the treatment of 61 anxious outpatients showed few drug differences. Diazepam treated patients improved significantly more early in the trial, according to a few psychometric measures. They also had significantly fewer complaints of drowsiness. By 6 weeks, the medicines appeared about equal in efficacy. Practically no support was found for the position that doxepin may be more beneficial for anxious/depressive syndromes. In all patients, and also within the anxious/depressive subgroup, there were small mean differences on many criteria favoring doxepin at 6 weeks, but none reached significance. The doxepin group gained significantly more weight. It is noted that possible biasing influences were present requiring that the results be interpreted with particular caution. 26 references. (Author abstract modified)

002483 Karabanow, Oscar. Humber Memorial Hospital, Weston, Ontario, Canada **Double-blind controlled study in phobias and obsessions.** Journal of International Medical Research (Northampton). 5(Supplement 5):42-48, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive neuroses and phobic disorders in Montreal, May 1977, the efficacy and tolerability of clomipramine (Anafranil) in a double-blind study of 20 clinically depressed patients with obsessive-compulsive and phobic psychopathological traits is reported. The patients (of either sex aged between 18 and 65 years) were randomly allocated to treatment with clomipramine (50mg twice daily) or to treatment with an identical placebo. Patients were assessed at the commencement of the study and at 2 week intervals over the 6 week duration of the trial. By the methods of assessment used, clomipramine proved to be highly statistically significantly superior to placebo in relieving symptoms of obsession and phobia in depressed patients. 11 references. (Author abstract modified)

002484 Marks, I. Bethlehem Royal & Maudsley Hospital, Denmark Hill, London, England **Recent results of behavioural treatments of phobias and obsessions.** Journal of International Medical Research (Northampton). 5(Supplement 5):16-21, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive neuroses and phobic disorders in Montreal, May 1977, some recent results of the behavioral treatment of phobias and obsessions are presented. Utilizing the basic principle of exposure of the patient to the evoking stimulus seems an effective treatment for many but not all obsessional patients and phobic patients. The role of tricyclic drugs is at present being investigated. Similar results, using an exposure in vivo model, have been obtained in the management of phobias. Some reasons why patients do not comply with, or adhere to, treatment recommendations are put forward, and the question of the cost effectiveness of treatment is considered. (Author abstract modified)

002485 Marshall, W. K. Severalls Hospital, Colchester, England **Clinical experience in the treatment of phobic disorders.** Journal of International Medical Research (Northampton). 5(Supplement 5):65-70, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive and phobic disorders in Montreal, May 1977, clinical experience in the treatment of phobias is discussed. The use of parenteral and oral clomipramine is described with emphasis on the desirability of incorporating these and other techniques in a regime of parenteral therapy for hospital inpatients. Oral administration of clomipramine is recommended for use in the case of outpatients. 7 references. (Author abstract modified)

002486 Mirabi, Mohsen; Mathew, Roy J.; Claghorn, James L. Texas Research Institute of Mental Sciences, Houston, TX 77025 **When is a neuroleptic appropriate in psychoneurosis?** Current Therapeutic Research. 23(1):101-104, 1978.

In a 4 week double-blind study, trifluoperazine and placebo were compared in 90 patients with history of chronic anxiety. The Hamilton Anxiety Scale, New Physicians Rating List, and Profile of Mood States were the main measures of change used; a total of 74 patients completed the study. After 4 weeks, 62% of the trifluoperazine group and 40% of the placebo regimen reported improvement. Adverse reactions to the drug were substantially diminished among patients who received small dosages. It is concluded that trifluoperazine is effective in treatment of chronic anxiety patients also presenting with somatic symptoms. 3 references. (Author abstract modified)

002487 Munro, Alistair. Toronto General Hospital, Toronto, Ontario M5G 1L7, Canada **Two cases of delusion of worm infestation.** American Journal of Psychiatry. 135(2):234-235, 1978.

Case histories of patients who suffer from a single delusional belief regarding some aspect of their health and whose personality otherwise remains intact are discussed. It is noted that the presenting histories of most individuals with monosymptomatic hypochondriacal psychoses are remarkably similar. Often the patient is distressed to the point of anguish yet angrily refuses psychiatric help. Consequently, a great deal of patience is required from the attending physician or psychiatrist. A simple treatment using pimozide produces remission rather than cure. It is concluded that pimozide apparently does not help cases of depressive, organic, or neurotic etiology, so the diagnosis of monosymptomatic hypochondriacal psychoses must be made with considerable care. 10 references.

002488 no authors. no address **What use are endorphins?** World Medicine (London). 13(1):75, 1977.

The role of endorphins, endogenous polypeptides which bind to opiate receptors, in mental illness is briefly reviewed; and an NIMH study of the effects of naloxone in schizophrenic and manic-depressive (n=19) is summarized. Previous reports have suggested that endorphin levels may be associated with affective illness, and schizophrenia. However a recent NIMH study found no or only trivial clinical improvement in schizophrenic and manic-depressive patients following intravenous administration of the narcotic agonist, naloxone. Findings suggest endorphin levels in these patients are either not abnormal or are nonpathogenic. Further research of naloxone effects in catatonia and other neuromuscular symptomatology has been recommended.

002489 Rack, P. H. Lynfield Mount Hospital, Bradford, Yorkshire, England **Clinical experience in the treatment of obsessional states (2).** Journal of International Scientific Research (Northampton). 5(Supplement 5):81-90, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive neuroses and phobic disorders in Montreal, May 1977, 7 years of experience in the intravenous use of clomipramine for the treatment of obsessional states is reviewed. It is observed that there is no adequate classification of obsessive-compulsive phenomena and they frequently coexist with other psychiatric symptoms, notably depression. Good results have been obtained with clomipramine in the treatment of depression, and obsessive-compulsive/phobic states, and mixed pictures. The results in neuroses and personality disorders are poor. It is concluded that clomipramine is the treatment of choice for obsessive-compulsive disorders, with or without accompanying depression. 10 references. (Author abstract modified)

002490 Rickels, Karl; Case, Warren G.; Csanalosi, Irma; Pereira-Ogan, Jorge A.; Sandler, Kenneth R.; Schless, Arthur P. Psychopharmacology Research and Treatment Unit, Dept. of Psychiatry, University of Pennsylvania, Philadelphia, PA 19104 **Loxapine in neurotic anxiety: a controlled trial.** Current Therapeutic Research. 23(1):111-120, 1978.

To assess anxiolytic efficacy of loxapine, 135 anxious neurotic outpatients presenting with and without depression were administered loxapine (n=43), chlordiazepoxide (n=47), or placebo (n=45) for a 6 week period under double-blind conditions. The intake form, the Physicians Questionnaire, the Hamilton Anxiety Scale, the Hopkins Symptom Checklist, and the disposition form were used to assess treatment effects. While side-effects were generally minimal, loxapine produced more serious side-effects than chlordiazepoxide. Few significant treatment effects were found, nor were treatment effects significantly different during the first 4 weeks of the trial, although chlordiazepoxide tended to be more effective than loxapine. At the end of 6 weeks chlordiazepoxide produced some significant treatment effects and these slightly outweighed those produced by either loxapine or placebo. It is concluded that results do not support antianxiety effects of loxapine. 12 references.

002491 Singh, A. N.; Saxena, B.; Gent, Michael. Hamilton Psychiatric Institute, Hamilton, Ontario, Canada **Clomipramine (Anafranil) in depressive patients with obsessive neurosis.** Journal of International Medical Research (Northampton). 5(Supplement 5):25-32, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive neuroses and phobic disorders in Montreal, May 1977, the role of clomipramine (Anafranil) as the treatment of choice for obsessive-compulsive symptoms in depression is discussed on the basis of effects in 20 patients. The subjects were given clomipramine in a flexible dosage schedule over a 4 week period. The results were assessed on the basis of each patient's response with respect to obsession symptoms and severity, depression, anxiety, and phobia. From the responses of the subjects it would appear that clomipramine possesses a specific antiobsessional property which is distinct from its antidepressant property. The optimal therapeutic dose from this study appears to be in the range of 175mg to 225mg a day. Minor reversible adverse reaction gradually decreases with the increase of duration of treatment. 12 references. (Author abstract modified)

002492 Solyom, L.; Sookman, D. Dept. of Psychiatry, Allan Memorial Institute, McGill University, Montreal, Canada **A comparison of clomipramine hydrochloride (Anafranil) and behaviour therapy in the treatment of obsessive neurosis.** Journal of International Medical Research (Northampton). 5(Supplement 5):49-61, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive neuroses and phobic disorders in Montreal, May 1977, the efficacy of clomipramine was studied in comparison with the efficacy of two behavior modification techniques, flooding and thought stopping. Clomipramine had a substantial ameliorating effect on the number and severity of obsessional symptoms, reducing the total obsessive symptomatology by half. The trends suggested that the drug was as effective as flooding and more effective than thought stopping in reducing the ruminative symptoms, and was especially effective in reducing pervading doubt. It was considerably less effective than behavior therapy in reducing the compulsive symptoms. A combination of pharmacotherapy and behavior therapy is the optimal treatment of choice for ritualistic patients who are

almost always very ruminative, doubtful and highly anxious. Clomipramine had the most substantial anxiolytic effect of the three groups and seemed to be as effective as behavior therapy in reducing phobias. 12 references. (Author abstract modified)

002493 Stern, R. S.; Cobb, J. P.; Marks, I. M.; Jones, R. B.; Luscombe, D. K. Institute of Psychiatry, Maudsley Hospital, London, England **A preliminary report on clinical response and plasma levels of clomipramine and desmethylclomipramine in obsessive-compulsive neurosis.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):97-103, 1977.

To test the efficacy of a combination of clomipramine and behavior therapy in obsessive-compulsive neurosis, a double-blind study was conducted. The preliminary findings show that the patients handle clomipramine metabolically in the same way as depressed patients, and that 10 obsessional subjects with severe, chronic handicapping rituals were markedly improved by the combined therapy. Control subjects who received behavior therapy with placebo also improved: whether the combination therapy was superior is currently being analyzed. The final results will be assessed in relation to duration of behavior therapy and plasma levels of both clomipramine and desmethylclomipramine. 15 references. (Author abstract modified)

002494 Strzyzewski, Wlodzimierz; Kapelski, Zdzislaw; Sydor, Leszek; Rajewski, Andrzej. Katedra i Klinika AM, 27/33 Szpitalna ul., Poznan 60-572, Poland **/Dosage effects of imipramine on the psychopathologic and biologic indices of endogenous depressive syndromes./** Wplyw imipraminy na psychopatologiczne i biologiczne wykladniki endogennych zespolow depresyjnych w zaleznosci od sposobu dawkowania. Psychiatria Polska (Warszawa). 11(3):379-380, 1977.

A letter to the editor reporting the relative merits of massive initial dosing versus gradual dosing of patients with thymoanaleptic drugs in the treatment of depression is presented based on study of imipramine given to two groups of 10 patients each. One group received the normal day of treatment. The second group received the maximal dosage on the first day of treatment. Results indicate that the group receiving the heavy initial imipramine dosage responded much better to the treatment.

002495 Vaisanen, E.; Naarala, M.; Kontiainen, H.; Merilainen, V.; Heikkila, L.; Malinen, L. Psychiatric Clinic, Oulu University Central Hospital, SF-90220 Oulu 22, Finland **Maprotiline and doxepin in the treatment of depression: a double-blind multicentre comparison.** Acta Psychiatrica Scandinavica (Kobenhavn). 57(3):193-201, 1978.

Maprotiline (Ludiomil) and doxepin were compared in the treatment of depression in a double-blind multicenter trial. Four centers and 95 inpatients and outpatients took part in the trial. The severity of depression was evaluated with the aid of a visual analogue scale and nine target symptoms. Both maprotiline and doxepin diminished neurotic as well as psychotic depression significantly. The mean time of onset of action was 7.0days in the maprotiline group and 7.7days in the doxepin group. No statistically significant differences in antidepressive effect were found between the treatments. Two patients in the maprotiline group and four patients in the doxepin group discontinued the treatment because of unwanted effects, one patient in each group because of lack of efficacy and nine patients due to reasons not related to the treatment. 14 references. (Author abstract)

002496 Villalobos, Alejandro. P.O. Box 2007, West Palm Beach, FL 33402 **A double-blind comparative clinical study of loxapine, diazepam, and placebo in hospitalized patients with various states of anxiety.** Current Therapeutic Research. 23(2):243-252, 1978.

The therapeutic efficacy of loxapine succinate is evaluated in a double-blind study of hospitalized patients with various states of severe anxiety. The 57 subjects were treated with loxapine, diazepam, or placebo in a 4 week, double-blind study. Evaluations of efficacy were based on the Hamilton Psychiatric Rating Scale for Anxiety, the Lipman Self-Rating Symptom Scale, the Nurses' Observation Scale for Inpatient Evaluation, Clinical Global Impression scale, and Patient's Self-Evaluation scale. Laboratory tests and vital signs measured at the end of the trial showed no differences from baseline values, and the side-effects of both active drugs were few, mild, and transitory. Both loxapine and diazepam were more effective than placebo for the treatment of anxiety, with loxapine being almost as effective as diazepam. 5 references. (Author abstract modified)

002497 Waxman, David. Dept. of Psychological Medicine, Central Middlesex Hospital, London, England **A clinical trial of clomipramine and diazepam in the treatment of phobic and obsessional illness.** Journal of International Medical Research (Northampton). 5(Supplement 5):99-110, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive neuroses and phobic disorders in Montreal, May 1977, findings of a double-blind comparative study of clomipramine and diazepam are given. Of the 58 original subjects, 41 completed the trial of which 14 were on clomipramine and 27 were on diazepam. Patients were assessed for phobias, obsessions, general psychiatric symptoms and side-effects, and each was rated on a special symptom inventory at 0, 2, 4 and 6 weeks of treatment. A General Health Questionnaire and Burns Questionnaire was completed for each patient at the beginning and end of the study. General level of anxiety for diffuse phobic anxiety and situational anxiety for illness and death fears responded better to clomipramine than to diazepam. In physiological accompaniments of obsessions, the change in score was greater on clomipramine, but not significantly so. Other psychiatric symptoms and the General Health Questionnaire showed the response to clomipramine to be significantly superior to that of diazepam. Global assessment showed significantly more progress on clomipramine than diazepam between weeks 4 and 6. 15 references. (Author abstract modified)

002498 Whitehead, William E.; Blackwell, Barry; Robinson, Ann. Department of Psychiatry, University of Cincinnati College of Medicine, 231 Bethesda Avenue, Cincinnati, OH 45267 **Effects of diazepam on phobic avoidance behavior and phobic anxiety.** Biological Psychiatry. 13(1):59-64, 1978.

The efficacy of diazepam for controlling phobic avoidance behavior and phobic anxiety and the potential usefulness of the behavioral approach measure for screening new antianxiety drugs was investigated in a double-blind study. The distance from the phobic object beyond which the subject would not approach and a rating of subjective anxiety at closest approach were made in 14 phobic patients immediately before and again 2 hr after 10mg oral diazepam or placebo. In the four Ss given diazepam, behavioral approach to the object was increased and subjective anxiety was decreased as compared to placebo. The method appears useful for early clinical screening of new drugs because it discriminates drug from placebo in a single short session using small groups and

because it employs a more objective dependent measure than self-report of subjective feeling states. Results are also taken to indicate the common practice whereby patients take minor tranquilizers on an as needed basis for the control of situational fears. 7 references. (Author abstract modified)

002499 Wootton, L. W.; Bailey, R. I. no address **The management of phobic disorders in general practice.** Journal of International Medical Research (Northampton). 5(Supplement 5):124-125, 1977.

In a paper presented at a scientific symposium on obsessive-compulsive neurosis and phobic disorders in Montreal, May 1977, the results of clomipramine treatment in over 2000 patients with a wide spectrum of neurotic disorders, using a flexible drug regime, is discussed. Common etiology was found in these patients and all could be said to be phobic, and as such many produced side-effects which could be predicted with accuracy and overcome. A method is described for inducing increased patient compliance and decreased dropout rate. 2 references. (Author abstract modified)

002500 Zisook, Sidney; Rogers, Peggy; McClelland, Mark; Faschingbauer, Thomas; Lloyd, Camille. Department of Psychiatry, University of Texas Medical School at Houston, Houston, TX **State-trait anxiety and anxiolytic treatment.** Current Therapeutic Research. 23(3):403-406, 1978.

The relative responsivity of a group of anxious outpatients to active medication (halazepam) and placebo was evaluated as a function of varying levels of state (situational) or trait (characterological) anxiety. All patients tended to do best on active medication. Higher initial state anxiety levels were negatively correlated with improvement in the placebo group, while higher initial trait anxiety scores were negatively correlated with improvement in the active drug group. Differential treatment responsivity of state and trait anxiety is described as a significant, unexplored area of clinical pharmacology deserving further investigation with larger samples, longer followup, and serial measures of state and trait anxiety. 9 references. (Author abstract modified)

002501 Zitrin, Charlotte Marker; Klein, Donald F.; Woerner, Margaret G. Long Island Jewish-Hillside Medical Center, PO Box 38, Glen Oaks, NY 11004 **Behavior therapy, supportive psychotherapy, imipramine, and phobias.** Archives of General Psychiatry. 35(3):307-316, 1978.

In a controlled outcome study of phobias, 111 adult patients (69% women, 31% men) received a course of 26 weekly treatment sessions consisting of behavior therapy and imipramine hydrochloride, behavior therapy and placebo, or supportive psychotherapy and imipramine. Patients were classified as agoraphobic, mixed phobic, or simple phobic. The majority of patients showed moderate to marked global improvement (70% to 86%, depending on rater). In agoraphobics and mixed phobics (both groups experiencing spontaneous panic attacks), imipramine was significantly superior to placebo. There was no difference between behavior therapy and supportive therapy, both resulting in high improvement rates. In simple phobic patients, there was a high rate of improvement with all treatment regimens, with no significant difference between imipramine and placebo or between behavior therapy and supportive therapy. Of 88 moderately to markedly improved patients followed up for 1 year after completing treatment, 83% maintained their gains and 17% relapsed. 17 references. (Author abstract modified)

11 DRUG TRIALS IN MISCELLANEOUS DIAGNOSTIC GROUPS

002502 Abuzzahab, F. S., Sr.; Merwin, G. E.; Zimmermann, R. L.; Sherman, M. C. University of Minnesota, Dept. of Psychiatry, Minneapolis, MN **A double-blind investigation of piracetam (Nootropil) versus placebo in the memory of geriatric inpatients.** Psychopharmacology Bulletin. 14(1):23-25, 1978.

A paper read at the annual meeting of the New Clinical Drug Evaluation Units of NIMH in Key Biscayne, FL, May 1977, on a double-blind investigation of the effects of piracetam (Nootropil) versus placebo on the memory of geriatric inpatients is presented. Fifty-six geriatric inpatients with mild deterioration of mental function were administered a psychometric battery to evaluate general mental functioning and short-term memory both before and after 2 months of piracetam treatment. No significant changes were noted in either clinical observations or biochemical analyses, and only ambiguous changes on psychometric tests were reported. Possible explanations for the lack of effects of piracetam on mental functioning in geriatric patients are offered. 25 references.

002503 Bark, Nigel. Rockland Research Institute, Orangeburg, NY 10962 **Clonazepam in the treatment of epilepsy in handicapped patients.** British Journal of Mental Subnormality (Birmingham). 23(45):84-87, 1977.

The use of clonazepam in the treatment of epilepsy in mentally handicapped patients is reported. Twenty patients with mainly myoclonic and akinetic seizures, were administered clonazepam. In nine the seizures ceased or were reduced by more than 50%. Adverse side-effects (mainly drowsiness and hypersalivation) occurred in 12 and, in 5, caused the drug to be stopped. The results are discussed and compared with other reports of the use of clonazepam and are found to be similar. 15 references. (Author abstract modified)

002504 Bielmann, P.; Levac, T. National Institute of Scientific Research, L.H. Lafontaine Hospital, 7401 Hochelaga St., Montreal, Quebec H1N 3M5, Canada **Can phenytoin be gradually withdrawn in patients with major motor epilepsy maintained on clonazepam and phenobarbital?** Current Therapeutic Research. 23(2):253-260, 1978.

Results from a 15 week controlled study in which phenytoin therapy was gradually reduced and finally stopped in a group of grand mal epileptic patients treated with clonazepam and phenobarbital are presented. A second group of patients whose phenytoin dose was maintained constant throughout the study served as controls. Although the increase in the number of seizures and diazepam emergency injections observed in the group without phenytoin did not reach statistical significance, the period of 5 weeks with complete phenytoin withdrawal would indicate that major motor epilepsy could not be adequately controlled by only clonazepam and phenobarbital. Further studies are required to assess the possibility of phenytoin reduction in this type of epilepsy. 12 references. (Author abstract modified)

002505 Branconnier, Roland J.; Cole, Jonathan O.; Gardos, George. Geriatric Psychopharmacology Unit, Boston State Hospital, Boston, MA **ACTH4-10 in the amelioration of neuropsychological symptomatology associated with senile organic brain syndrome.** Psychopharmacology Bulletin. 14(1):27-30, 1978.

A paper read at the annual meeting of the New Clinical Drug Evaluation Units of NIMH in Key Biscayne, FL, May 1977, on the fourth through tenth amino acid sequences of adrenocorticotropic hormone (ACTH 4 through 10) in the amelioration of neuropsychological symptomatology associated with senile organic brain syndrome is presented. In a double-blind crossover study, 18 volunteers over the age of 60 years who displayed neuropsychological symptomatology associated with senile organic brain syndrome were administered a battery of neuropsychological tests before and after drug or placebo administration. Results indicate that ACTH 4 through 10 is capable of improving the affective state in patients with mild to moderate senile organic brain syndrome, inducing changes in EEG and possibly enhancing retrieval from memory. While the mechanism of action remains unclear, it is hypothesized that this compound may affect nonspecific brain-stem arousal systems. 14 references.

002506 Brown, Calvin Reed. 4275 Whiteway, Salt Lake City, UT 84117 **The use benzodiazepines in prison populations.** Journal of Clinical Psychiatry. 39(3):219-222, 1978.

A review of the literature on benzodiazepine effects is presented together with a summary of two benzodiazepine studies in a Utah prison population; and contraindications and guidelines for the use of benzodiazepines in prison populations are discussed. A number of studies have indicated that benzodiazepines may result in increased anxiety, aggression, hostility, paradoxical rage reactions, lability of affect, and suicidal ideation in some patient populations. Two controlled studies in Utah State Prison populations provided further support for these findings, demonstrated that oxazepam is preferable to diazepam if a tranquilizer is indicated, and suggested that benefits derived from this class of drugs are often outweighed by negative effects in individuals exhibiting antisocial/criminal behaviors. On the basis of study findings, guidelines for the use of benzodiazepines in the behavior modification program at Utah State Prison were developed which included strict limitations on the prescription of and access to psychotropic medications and negative reinforcements for attempts by inmates to obtain such drugs through manipulation of the program staff. 11 references.

002507 Christodoulou, G. N. Athens University, Department of Psychiatry, Eginition Hospital, 74 Vasilissis Sofias Avenue, Athens, Greece **Course and prognosis of the syndrome of doubles.** Journal of Nervous and Mental Disease. 166(1):68-72, 1978.

The course and prognosis of 20 patients with the syndrome of doubles (syndrome of Capgras, syndrome of Fregoli, syndrome of intermetamorphosis, syndrome of subjective doubles) were studied. The onset of the syndrome occurred either synchronously, or at a later stage than the onset of the associated psychosis. The syndrome failed to remit following psychopharmacotherapy or EST in seven of the 20 cases, and in the others remission occurred either synchronously with or later than remission of the basic psychosis. In all cases of depression, the syndrome cleared shortly after remission of the depressive illness. It was, however, more persistent than the accompanying psychosis in schizophrenic patients with the Capgras variety. Relapse of the basic psychosis condition, in the setting of which the syndrome had originally developed, was invariably accompanied by reappearance of the syndrome. 17 references. (Journal abstract modified)

002508 Corsini, Giovanni U.; Onali, Pierluigi, Masala, Carmelo; Cianchetti, Carlo; Mangoni, Alfonso; Gessa, Gianluigi. Department of Mental and Nervous Diseases and Pharmacology, University of Cagliari, Cagiliari, Italy **Apomorphine hydrochloride-induced improvement in Huntington's chorea.** Archives of Neurology. 35(1):27-30, 1978.

The beneficia effects brought about by apomorphine hydrochloride in Huntington's chorea were investigated. Four patients affected by Huntington's chorea with a well defined family history of the disease were injected intramuscularly with apomorphine hydrochloride in nonemetic doses. Soon after treatment, all patients showed a marked decrease in abnormal involuntary movements. Pretreatment with ahloperidol or supiride 30 minutes prior to apomorphine treatment, prevented the therapeutic effect of this compound. It is suggested that apomorphine-induced improvement in Huntington's Chorea is mediated by the stimulation of a special kind of dopamine receptor, leading to inhibition of the activity of dopaminergic neurons. 19 references. (Author abstract modified)

002509 Davis, Kenneth L.; Berger, Philip A. V.A. Hospital, 3801 Miranda Avenue, Palo Alto, CA 94304 **Pharmacological investigations of the cholinergic imbalance hypotheses of movement disorders and psychosis.** Biological Psychiatry. 13(1):23-49, 1978.

The hypotheses of relative cholinergic underactivity in Huntington's disease, tardive dyskinesia, mania, and schizophrenia were pharmacologically investigated using physostigmine and choline chloride. Intravenous physostigmine improved the involuntary movements of all of four patients with tardive dyskinesia and three of six patients with Huntington's disease. Physostigmine infusion also decreased manic symptoms in six of nine patients with mania but had no beneficial effects in three patients with schizophrenia. It is suggested that precursor loading with choline chloride may increase brain acetylcholine levels and central cholinergic activity. In patients with movement disorders a transient improvement during physostigmine infusion predicted a positive response to a trial of oral chloride. One manic patient may have been improved by choline chloride, however choline chloride did not improve symptoms in four of six schizophrenic patients. Chronic treatment with oral choline chloride increased plasma levels of choline during administration and for approximately 48 hr after discontinuation of treatment. These results with physostigmine support the hypotheses of cholinergic underactivity in Huntington's disease, tardive dyskinesia, and mania. Agents which might chronically increase cholinergic activity such as choline chloride should be further tested in these disorders. 57 references. (Author abstract modified)

002510 Fahn, Stanley; Calne, Donald B. Neurological Institute, 710 West 168th Street, New York, NY 10032 **Considerations in the management of parkinsonism.** Neurology. 28(1):5-7, 1978.

A decade of experience with levodopa in treatment of parkinsonism is reviewed. The value of the drug has been confirmed, however common late adverse reactions have also been revealed, some of which are difficult to overcome once established. To delay the onset of such problems, it is becoming common practice to withhold levodopa until the severity of symptoms warrants its use, and then to treat patients with the minimum dose that will restore adequate motor function, considering the patient's work, personality, and social situation. Further research on dopaminergic agonists' ability to alleviate any of the current difficulties in the treatment of parkinsonism is suggested. 19 references.

002511 Gillis, John S.; Moss, Carl D. Oregon State University, Corvallis, OR 97331 **An experimental study of the effects of amitriptyline-perphenazine and amitriptyline-haloperidol combinations on interpersonal learning.** Current Therapeutic Research. 23(2):261-270, 1978.

The effects of two frequently used combinations of antipsychotic and antidepressant medications (amitriptyline/perphenazine and amitriptyline-haloperidol) were assessed on measures of conflict resolution and interpersonal learning. Thirty-two patients were selected for inclusion in the study on the basis of their present chemotherapeutic regimens. Several statistical indices of performance were generated by the interpersonal tasks used. The performance of patients receiving an amitriptyline/haloperidol combination was superior to that of patients being treated with amitriptyline and perphenazine on all measures. These differences reached statistically significant levels on one measure of conflict resolution and closely approached significance on another. 21 references. (Author abstract)

002512 Gustafson, Lars; Risberg, Jarl; Johanson, Margareth; Fransson, Margareta; Maximilian, V. Alexander. Lab. of Neuropsychology, Dept. of Psychiatry, University Hospital, Lund, Sweden **Effects of piracetam on regional cerebral blood flow and mental functions in patients with organic dementia.** Psychopharmacology (Berlin). 56(2):115-117, 1978.

The effects of piracetam (Nootropil, UCB-6215) on mental functions and on regional cerebral blood flow (rCBF) were investigated in eight patients in the presenile age who displayed symptoms of moderate dementia. The double-blind crossover design included nine measurement occasions, each involving rCBF measurement by the 133-Xe inhalation method, ratings of symptoms of dementia, personality changes, and side-effects, and a psychometric investigation. Three investigations were included in each of three treatment periods. The first investigation in a period was made without medication. Then either placebo or piracetam 4.8g/day or 9.6g/day was given during four weeks with measurements after 2 weeks and 4 weeks. There was intervals of 4 weeks without medication between the treatment periods. Piracetam had no significant effect on either mental functions or rCBF. 19 references. (Author abstract)

002513 Ignatowicz, Lucja; Ignatowicz, Roman; Wdowiak, Maria Wanda; Jaremko, Aleksander. Klinika Psychiatryczna PAN, ul. Broniewskiego 32, 71-460 Szczecin, Poland /**Azaphen in the treatment of enuresis in children.**/ Azaphen w terapii moczenia mimowolnego u dzieci. Psychiatria Polska (Warszawa). 11(1):29-33, 1977.

Research on the use of azaphenin treatment of enuresis in children is reported. Azaphen was given to 46 children, age 6 to 15, with bedwetting problems. The dose varied from 25 to 50mg per day, in isolated cases the dose was increased up to 75mg per day. The treatment lasted from 6 to 8 weeks. Good and very good results were observed in 26 cases. On the basis of their observations the authors concluded that Azaphen acts favorably in cases of psychogenic enuresis. Psychotropic effect of the drug is usually supplemented with its antineurotic effect in the third and fourth week of treatment. Children showed good tolerance to the drug. 26 references. (Journal abstract modified)

002514 Knapp, Richard B.; Boyd, Edwyn L.; Linsenmeyer, George; Linet, Otto I. Dept. of Anesthesiology, West Virginia University Medical Center, Morgantown, WV 26506 **Evaluation of triazolam, flurazepam, and placebo as hypnotic agents in pre-surgical patients.** Current Therapeutic Research. 23(2):230-235, 1978.

Two investigations on the cardiopulmonary safety and efficacy of triazolam, a benzodiazepam derivative, when used as a presurgical hypnotic agent are presented. In a double-blind evaluation of 18 medical student volunteers, it was determined that there were no statistically significant differences in stroke volume, cardiac output, CO2 response, minute and tidal volumes, blood pressure, or heartrate after oral intake of 0.5mg or 1.0mg of triazolam or placebo. A second double-blind study of 120 patients compared the hypnotic effects of 0.5mg and 1.0mg triazolam with 30mg flurazepam and placebo, all ingested orally. Triazolam achieved onset of sleep in less than 30 minutes and duration of sleep of longer than 6 hours in 41 out of 60 patients, a statistically significant result. In comparing rapidity of onset of sleep, flurazepam offered no advantage over placebo in this study. 6 references. (Author abstract modified)

002515 Koziel, Halina; Kuran, Wlodzimierz; Zakrzewska, Franciszka. Instytut Psychoneurologiczny, Sobieskiego 1/9, 02-957 Warsaw, Poland /**Somatosensory evoked potentials in patients with Parkinson's syndrome during treatment with L-Dopa and decarboxylase inhibitor.**/ Somatosensoryczne potencjaly wywolane u chorych z zespolem parkinsonowskim w przebiegu leczenia L-DOPA i inhibitorem dekarboksylazy. Neurologia i Neurochirurgia Polska (Warszawa). 11(1):73-80, 1977.

The effects of L-DOPA with decarboxylase inhibitor on evoked somatosensory potentials were studied in eight patients with idiopathic Parkinson's syndrome, two with postinflammatory syndrome and two with atherosclerotic parkinsonism. The potentials were recorded by a 2 bipolar technique contralaterally from the surface of the cranium in the region of the sensorimotor area in response to supramaximal electrical stimulation of the median nerve at wrist level. The investigations were carried out three times: before beginning of treatment, and usually 14 days and 67 days after beginning. Latency and amplitude of early components (wave III), late components (wave IV and V) and very late components (wave VI, VII and VIII) were determined. Results showed changes in latency and amplitude during treatment were statistically not significant. Other wave characteristics are discussed. It is suggested that differences in changes of latency and amplitude in the left and right hemispheres during administration of L-DOPA may be due to differences in neuroanatomical changes in both hemispheres, which had not been demonstrated clinically in advanced cases of the disease. 16 references. (Journal abstract modified)

002516 Krishna, N. Rama; Taylor, Michael A.; Abrams, Richard. Dept. of Psychiatry and Behavioral Sciences, University of Health Sciences/Chicago Medical School, Building 50, Chicago, IL 60064 **Combined haloperidol and lithium carbonate in treating manic patients.** Comprehensive Psychiatry. 19(2):119-120, 1978.

The experiences of 28 patients who received the combination of haloperidol and lithium carbonate for the treatment of acute mania are discussed. There were eight men and 20 women ranging in age from 19 to 66 years. The mean lithium dosage was 1390mg/day and the mean haloperidol dosage was 48mg/day. A total of 24 patients who received combined therapy were discharged either on the combination or on lithium maintenance alone. The remaining four patients did not respond adequately to the combined therapy and received ECT. Extrapyramidal side-effects of treatment were transient, generally mild to moderate, and responded to benztropine. The

presence of classical schizophrenic symptoms such as first rank Schneiderian symptoms was not associated with any adverse response to combined lithium and in high doses proved to be quite clinically effective and without permanent side-effects. 5 references.

002517 Lairy, G. C.; Goas, A. Le. no address **Epilepsy in child psychiatry. Effects of treatment by dipropylacetic acid.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):557-558, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, the effects of treatment of epilepsy in children with dipropylacetic acid (DPA) are described. DPA proved effective in a series of neuropsychiatric disorders of children, mainly because of its metabolic activating properties. The subjects were 34 children selected from a series of 75, previously unsuccessfully treated by classical anticonvulsants, and given DPA for over 2 years. In 15 cases with sequelae of early organic brain lesions, positive effects were obtained in 12. In 19 cases of epilepsy associated with psychosis, some degree of clinical and EEG improvement was obtained in 14. The clinical changes consisted of reduction of seizures in both groups; moreover, a marked increase of mental efficiency, attentiveness and school performance was observed in the first group and a better quality of awareness, social contact and communication in the second facilitated the process of rehabilitation of the children. Besides the reduction of paroxysmal discharges, the EEG changes consisted of an improvement of the temporospatial distribution of the background rhythms: alpha-activity more regular, more limited to the posterior leads, and better blocked by eye opening. In both groups and especially the second, the positive effects of DPA were not immediate, as in petit mal, but might require several months to develop. (Author abstract modified)

002518 Lukasiewicz, Kazimierz. Oddzial Neurologii Klinicznego Szpitala Zespolonego, ul. Czerniakowska 231, 00-416 Warsaw, Poland **/Combined treatment with L-Dopa and Parcopan in Parkinson's disease.** Skojarzone leczenie choroby Parkinsona L-Dopa i Parkopanem. Wiadomosci Lekarskie (Warszawa). 30(1):775-777, 1977.

A study of combined treatment with L-Dopa and Parcopan in Parkinson's disease is presented. A group of 33 patients, almost all of whom were previously treated with Parcopan, were given L-Dopa in addition to determine whether stopping Parcopan would affect the patient adversely, or whether L-Dopa as an adjunct could be more effective at lower than usual doses. Optimal daily dosage of L-Dopa which could be effective with minimal side effects was sought. The treatment, which lasted between 3 to 11 weeks, produced marked improvement in all cases by the 10th to 14th days. Results indicate that the combination was effective in 77% of the cases, with a significant reduction in Parcopan side effects. 10 references.

002519 Major, L. F.; Goyer, P. F. Clinical Neuropharmacology Branch, NIMH, Bldg. 10, Rm. 35229, 9000 Rockville Pike, Bethesda, MD 20017 **Effects of disulfiram and pyridoxine on serum cholesterol.** Annals of Internal Medicine. 88(1):53-56, 1978.

The effects of disulfiram and pyridoxine on serum cholesterol were studied in alcoholic persons. It was found that 500mg/day of disulfiram raised serum cholesterol levels in alcoholic persons from a mean of approximately 193mg/dl to approximately 227.2mg/dl after 3 weeks and to 264mg/dl after 6 weeks. This increase was not seen in a group taking pyridoxine 50mg/day in addition to disulfiram 500mg/day. In contrast to the disulfiram and disulfiram/pyridoxine treatment groups, control groups receiving pyridoxine alone or no drug, had a 33mg/dl reduction in serum cholesterol during the first 3 weeks of abstinence, a finding consistent with other evidence showing a rapid decrease in serum lipids on abstinence from alcohol. Patients taking disulfiram 250mg/day, with or without pyridoxine, did not have this expected decrease in serum cholesterol. Since increased serum cholesterol is one of the risk factors in coronary heart disease, chronic disulfiram therapy may increase the incidence of arteriosclerotic cardiovascular disease, as has been the case with chronic exposure to carbon disulfide, a principal metabolite of disulfiram. 43 references. (Author abstract)

002520 McIntyre, H. B.; Firemark, H. M.; Cho, A.; Jenden, J. no address **Electrophysiological studies and amphetamine metabolism in hyperactive children.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):468, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, electrophysiological studies and amphetamine metabolism in hyperactive children are described. Thirty hyperactive children were treated in double-blind fashion with d-amphetamine, l-amphetamine, and placebo. Using gas chromatography/mass spectrometry the concentrations of each amphetamine isomer in blood and urine were measured for 24 hours at the start and finish of each 3 week treatment cycle. Blood levels of both drugs were maximal by 3 hours after a 5mg dose. The average serum half-life was 9 hours. There were no significant differences between d-amphetamine and l-amphetamine in absorption and excretion. Behavioral assessments were made by an investigator's clinical examinations and by parents' and teachers' use of Conner's and Burke's questionnaires. Approximately 1/5 of the subjects responded to placebo and 5/6 of these were diagnosed as other than hyperactive at the time of the study. An approximately equal proportion of the hyperactive subjects responded to the l-amphetamine as responded to the d-amphetamine. Responders and nonresponders did not differ in drug half-life. Changes in EEG power spectral analysis, auditory evoked potentials, and visual evoked potentials in respect to serum drug levels and behavioral response were studied. (Author abstract modified)

002521 McLeod, Malcolm N.; Fisher, Paula. Duke University Medical Center, Durham, NC 27706 **Pavor nocturnus in a schizophrenic patient: a review and case study.** American Journal of Psychiatry. 135(2):235-236, 1978.

The use of phenothiazines in controlling chronic schizophrenia and night terror in a 28-year-old male was evaluated. A referring psychiatrist described the patient as having auditory hallucinations, and extensive paranoid delusions. The staff diagnosed the problem as pavor nocturnus with associated destructive behavior and not as schizophrenia. Chlorpromazine controlled the schizophrenic symptoms but did not affect his night terrors and so diazepam was added. A complete remission of the night terrors followed. The treatment has been continued at home, and after 1 year no recurrence has been found. 6 references.

002522 Mendelson, Wallace B.; Gillin, J. Christian; Wyatt, Richard Jed. NIMH, Bldg. 10, Rm 3N224, NIH, Bethesda, MD 20014 **Narcolepsy: diagnosis and treatment. (Unpublished paper).** Bethesda, MD, NIMH, 1978. 15 p.

The diagnosis and treatment of narcolepsy are described. Narcolepsy is characterized by excessive daytime sleepiness and brief sleep attacks. Auxiliary symptoms include cataplexy, sleep paralysis, and hypnopompic and hypnogogic hallucinations. Psychologically, the patient is likely to feel depressed and suffer a sense of frustration and failure. Narcoleptic symptoms may appear from childhood to middle age. In treatment, sleep attacks and cataplexy should be handled separately, tailoring the therapeutic goal to the symptoms which are most disabling to the patient. Sleep attacks respond to the analeptics, methylphenidate and dextroamphetamine. Possible problems include nocturnal sleep loss if the analeptics are administered late in the day, and the development of tolerance. A drug holiday can be helpful in the latter case. The tricyclic antidepressants are recommended for treatment of the auxiliary symptoms. Finally, the patient can be advised to try taking several 10 minute naps daily, to reduce intake of sweets and carbohydrates, and to develop regular nocturnal sleeping habits and avoid activities which may cause nocturnal sleep loss. 9 references.

002523 Nair, N. P. V.; Schwartz, G. Research Department, Douglas Hospital Centre, 6875 LaSalle Boulevard, Montreal, Quebec H4H 1R3, Canada **Triazolam in insomnia: a standard-controlled trial.** Current Therapeutic Research. 23(3):388-392, 1978.

A 7-day comparative clinical trial investigating the comparative activity and efficacy of 0.5mg triazolam and 30mg flurazepam was conducted in 20 insomniacs utilizing a daily self-rating questionnaire. Both groups significantly improved on all sleep parameters. Significant differences between the groups favoring triazolam were obtained in number of hours slept, depth of sleep, and perceived usefulness of the drug as a hypnotic; while the flurazepam group perceived their sleep as significantly more restful. Laboratory results were normal and side-effects not significant. 9 references. (Author abstract modified)

002524 Okawa, K. Kay. Bountiful Professional Plaza, 1480 South Orchard Drive, Bountiful, UT 84010 **Comparison of triazolam .25 mg and flurazepam 15 mg in treating geriatric insomniacs.** Current Therapeutic Research. 23(3):381-387, 1978.

A 7 day, double-blind clinical trial was conducted to assess the therapeutic effectiveness of triazolam 0.25mg, compared with that of flurazepam 15mg, in treating insomnia in geriatric patients. Seventy-one patients were treated, 36 with triazolam and 35 with flurazepam. The results showed that patients on triazolam experienced significant improvement in sleep onset, duration of sleep, and reduction of night-time awakenings. Patients on flurazepam experienced significant improvement in the duration of sleep. A comparison of the two treatments showed triazolam was significantly better than flurazepam on how much the medication helped the pateints sleep, and significantly fewer triazolam patients reported having dreams. Triazolam was also rated higher than flurazepam on all other sleep measures, however, the differences were not significant. Fifteen triazolam patients and 13 flurazepam patients reported side-effects. The same variety of side-effects occurred in each treatment group with drowsiness being reported most often. Laboratory evaluations and poststudy physical examinations showed no deleterious effects over the 1 week treatment period. 11 references. (Author abstract modified)

002525 Perris, Carlo. Department of Psychiatry, Umea University, S-90185 Umea 6, Sweden **Morbidity suppressive effect of lithium carbonate in cycloid psychosis.** Archives of General Psychiatry. 35(3):328-331, 1978.

The possible morbidity suppressive effect of lithium carbonate on cycloid psychosis was investigated in 30 patients who had suffered from recurrent psychotic episodes. The patients were followed up from 1 to 8.5years after starting lithium treatment. In the analysis, patients were divided into those who took lithium regularly and those who took it irregularly, the division being based on the lithium plasma levels at the periodic control examinations. Results indicate a significant reduction in morbidity in patients with a carefully controlled and well managed course of treatment, while there is slight nonsignificant increase in the number of psychotic episodes and in total morbidity time in patients with an unsatisfactory course of treatment (irregular ingestion of lithium). In both groups of patients a slight decrease in hospitalization times is also found, with the decrease being greater for those patients with a satisfactory course of treatment. While results of a mirror type study such as this are not totally conclusive, results provide some support that well conducted lithium maintenance treatment has a favorable morbidity suppression effect in cycloid psychosis patients. 17 references. (Author abstract modified)

002526 Potolicchio, S. J., Jr.; Gut, A. M.; Beaumanoir, A. no address **Alertness in epileptics: pharmacological and psychometric study.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):541, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, pharmacological and psychometric studies of alertness in epileptics are discussed. Correlations between serum levels of several anticonvulsants and neuropsychological performance in a population of 54 epileptics were established. During a double-blind crossover study with dipropylacetate (DPA), diphenylhydantoin (DPH) and phenobarbital involving telemetry and serum level determinations, a battery of neuropsychological tests was administered to the patient population. The psychometric tests included the Wechsler-Bellevue Intelligence Scale, the Stambach battery for motor skills, the Bender test for spatial orientation, the Stambach tests for rhythm, and two memory tests by Rey. Blood was drawn for serum level measurements at the end of each testing session. A comparative study of psychometric test scores revealed an unfavorable effect of phenobarbital, used alone or in association with DPA and DPH, on alertness. DPA was found not to affect psychometric scores in DPA/placebo treated patients. The results demonstrate the inefficacy of phenobarbital or the association of DPA and phenobarbital in those seizure types involving primarily a reduction in vigilance. (Author abstract modified)

002527 Remschmidt, H.; Mewe, F.; Mewe, G.; Dauner, I.; Merschmann, W. Abteilung fur Psychiatrie und Neurologie des Kindes- und Jugendalters, Freie Universitat Berlin, Nussbeumallee 36, D-1000 Berlin 19, Germany **/Effect of thioridazine (Melleril-Sandoz) on psychomotor function, concentration, and reactivity in children with behavior disorders./** Der Einfluss von Thioridazin (Melleril-Sandoz) auf Psychomotorik, Konzentrationsverhalten und Reaktionsvermogen bei verhaltensgestorten Kindern. Pharmakopsychiatrie/Neuro-Psychopharmakologie (Stuttgart). 10(1):1-9, 1977.

Thioridazine was compared with placebo in a double-blind study of 26 hospitalized children, 6 to 16 years old, showing behavior disturbances. The 23 boys and 3 girls had IQs ranging from under 80 to over 120. Diagnoses were aggressive behavior without brain damage in 13, early childhood brain damage in 5, neglect syndrome and disturbances of contact in

6, and encopresis and enuresis in 2. Most of the patients had other symptoms such as school difficulties, disturbances of concentration, speech disorders, anxiety, and headaches. Thioridazine was given for 4 wks. Patients were evaluated by the Brickenkamp d2 test which measures attention capacity, a tapping test, a tracing test, and the Vienna determination apparatus test. The drug group performed significantly better on the tapping test and in concentration. Thioridazine seemed to alter visuomotor information processing and to improve performance in simply structured motor tasks, but it makes complex choice reactions more difficult. 19 references.

002528 Richmond, Janet S.; Young, J. Richard; Groves, James E. Psychiatric Walk-In Clinic, Boston V.A. Clinic, 17 Court Street, Boston, MA 02108 **Violent dyscontrol responsive to d-amphetamine.** American Journal of Psychiatry. 135(3):365-366, 1978.

A case history of violent dyscontrol in a 30-year-old male which was responsive to d-amphetamine is reported. It is suggested that individuals who would ordinarily receive the diagnosis of antisocial personality and who have a childhood history resembling that of minimal brain dysfunction may respond to therapeutic trials of imipramine, methylphenidate, or d-amphetamine, especially if the patient reports calming on stimulant drugs. A positive result may be indicated by: 1) maintenance of weight and sleep; 2) lack of escalation of dosage and manipulation for extra medication; 3) subjective report of better concentration; 4) better interpersonal relationships; 5) family ratings of diminished dyscontrol; and 6) evidence of improved social adjustment in areas such as work performance and problems with the law. 6 references.

002529 Schmidt, D.; Goldberg, V.; Guelen, P. J. M.; Johannessen, S.; Kleijn, E. V. D. Klinikum Charlottenburg, Freie Universitat, Berlin, Germany **Evaluation of a new immunoassay for determination of phenytoin and phenobarbital: results of a European collaborative control study.** Epilepsia. 18(3):367-374, 1977.

The results of antiepileptic drug determinations carried out by seven European laboratories on common serum samples are summarized. The performance of a new enzyme multiplied immunoassay technique (EMIT) was compared with other current methods, namely gas liquid chromatography and thin layer chromatography, for the determination of phenytoin and phenobarbital in serum. There was good agreement among gas chromatography, thin layer chromatography, and EMIT results. The rapid analysis of small samples, made possible by the EMIT system, could have beneficial effects on the treatment of epilepsies. 11 references.

002530 Seipel, John H.; Fisher, Robert; Blatchley, Robert J.; Floam, Judith E.; Bohm, Mark. no address **Rheoencephalographic and other studies of betahistine in humans. IV. Prolonged administration with improvement in arteriosclerotic dementia.** Journal of Clinical Pharmacology. 17(2-3):140-161, 1977.

The efficacy of betahistine, a potent cerebral vasodilator, in patients with arteriosclerotic dementia was studied in an open trial with six patients and a placebo controlled double-blind test with 30 patients. The betahistine was given orally t.i.d.,for 6 mos. All patients were evaluated on the Nurses' Observation Scale for Inpatient Evaluation, and psychometric tests were used when possible. The six patients in the open study were additionally evaluated by intracranial rheoencephalography. Four patients had to be dropped from the study for physical illness and two for noncooperation. Betahistine gave rise to significant cerebral and scalp arterial vasodilatation and circulatory improvement, and which in turn caused significant global improvement in patient behavior. Improvement was sometimes detected within 2 wk or less, reached a maximum by 90 days, and was sustained by continued therapy. No adverse medication effects were noted. 28 references.

002531 Serban, G. Community Project, NYU - Bellevue Hospital, New York, NY **New approach to the rehabilitation of the card core drug addict (heroin methadone addicts): a pilot community study.** Journal of Clinical Psychiatry. 39(2):111-116, 1978.

A new approach to the rehabilitation of heroin and methadone addicts, utilizing antidepressants and anxiolytics during the detoxification phase, is described. It is noted that the limitation of the methadone maintenance program has pressed for a reevaluation of our understanding of the underlying causes of addiction. Apparently, one of the underlying causes or end result produced by the drug itself is that of depression. It explains why the addicts try to maintain to the maximum euphoric state and are unwilling to rehabilitate. A pilot study was conducted for the treatment of exmethadone addicts with large dosages of antidepressants and anxiolytics. Out of 117 exmethadone and soft drug addicts treated with antidepressants and anxiolytics, 46% exmethadone and 46.3% soft drug abusers failed to become abstinent. The failures were basically related to the management of treatment. It is maintained that the study suggests a possibility for detoxification from methadone and control of relapse by antidepressants and anxiolytics. 18 references. (Author abstract modified)

002532 Sheard, Michael H.; Marini, James L. Connecticut Mental Health Center, New Haven, CT 06508 **Treatment of human aggressive behavior: four case studies of the effect of lithium.** Comprehensive Psychiatry. 19(1):37-45, 1979.

Four case histories of male inmates whose violent impulsive aggressive behavior was treated with lithium during a double-blind drug trial are reported. Predrug personality assessments included the MMPI, Eysenck Personality Inventory, Buss-Durke Hostility Inventory and Lykken Sociopathy Scale. During the 3-month drug trial, changes in aggressive behavior were assessed by a monitoring of the number and type (major or minor) of reports of infraction issued by the correctional institution's staff. Monthly test batteries were also administered, including the Multiple Affect Adjective Check List, the Arrow Dot Test, Common Annoyances Test, Rosenzweig Picture Frustration Test, and the Hostility and Direction of Hostility subset of the MMPI. Additionally, weekly interviews with the subjects were conducted which permitted self-assessment of their progress and staff assessment of their affects and attitudes. The four lithium responder cases are used to illustrate that with lithium treatment, anger (once aroused) does not escalate in the way it customarily does in these violent individuals. In some individuals the drug also promoted self-reflection and mood depressions. The subjects were unaware of the changed performance due to the drug's effect in their self-assessment of their behavior. 16 references.

002533 Sprague, Robert L. no address **Psychopharmacotherapy in children.** Research report, NIMH Grant MH-18909, 1977. 14 p.

Public controversy and other issues arising from psychopharmacotherapy with children are discussed in the context of a review of pharmacotherapy of hyperactive and mentally retarded children. Prevalence of drug usage by hyperactive and mentally retarded children is reported, and the

effects of psychotropic drugs on school performance of the hyperactive child and drug treatment of the mentally retarded child are reviewed. The public impact of these controversies and legal actions concerned with child psychopharmacotherapy are discussed. 40 references.

002534 Swanson, James; Kinsbourne, Marcel; Roberts, Wendy; Zucker, Kenneth. Neuropsychology Research Lab., Hospital for Sick Children, 555 University Ave., Toronto, Ontario M5G 1X8, Canada **Time-response analysis of the effect of stimulant medication on the learning ability of children referred for hyperactivity.** Pediatrics. 61(1):21-29, 1978.

A method for obtaining behavioral time response information for a short acting psychotropic drug (methylphenidate) that is used to treat behaviorally hyperactive children is described. A laboratory learning task was used to document that between 1 and 2 hours after the administration of a single dose of methylphenidate, the drug exerts its maximum effect on performance in a learning task in the laboratory. This effect on cognitive performance dissipates within the same day. This rapid and transient effect of methylphenidate makes it possible to classify patients in a single day into those who respond favorably and those who respond adversely to the drug in terms of its effect on cognitive behavior. 41 references. (Author abstract)

002535 Trimble, Michael. National Hospital, Queen Square, London WC1, England **Use of depot tranquillisers in psychiatric disorders.** British Medical Journal (London). No. 6101:1541, 1977.

The use of depot tranquilizers (fluspirilene) with five nonschizophrenic psychiatric patients who either had psychiatric disorders which were not responding to conventional oral medications or had long standing psychiatric disorders that had failed to respond to other treatments, is described. Three patients had either long standing or acute anxiety disorders; one suffered from anorexia nervosa; one suffered from chronic dpressive disorder. Within 2 to 6 weeks of treatment all patients were much improved.

002536 Waziri, Rafiq. University of Iowa, Iowa City, IA 52242 **Catatonia.** Journal of the American Medical Association. 238(23):2495, 1977.

The primacy of the usefulness of electroconvulsive therapy (ECT) in lethal catatonic states is emphasized. It is recommended that if a neuroleptic must be used in the treatment of the psychiatric condition underlying the catatonia, then cautious doses of drugs such as haloperidol (Haldol) and trifluoperazine hydrochloride (Stelazine) should be used since these have fewer anticholinergic and hypotensive properties. It is noted that these drugs may worsen the catatonic state. 3 references.

002537 Will, J. C.; Abuzzahab, F. S., Sr.; Zimmermann, R. L. University of Minnesota Hospitals, Minneapolis, MN **The effects of ACTH4-10 versus placebo in the memory of symptomatic geriatric volunteers.** Psychopharmacology Bulletin. 14(1):25-27, 1978.

A paper read at the annual meeting of the New Clinical Drug Evaluation Units of NIMH in Key Biscayne, FL, May 1977, on the effects of the fourth to tenth amino acid sequence of adrenocorticotropic hormone (ACTH) versus placebo on the memory of symptomatic geriatric volunteers is presented. This small portion of ACTH (fourth to tenth amino acid sequence) does not have the usual metabolic effects found with ACTH, such as effects on adrenal steroid hormone production, endocrine function, or carbohydrate and fat metabolism in the rat. The lack of effect of ACTH4-10 on the memory of symptomatic geriatric volunteers was attributed to: 1) length of action of the drug was too short, so peak effects had already worn off by the time of testing; 2) dosage was inadequate; and 3) the population was not sufficiently impaired to permit measure of improvement with ACTH 4 through 10. 21 references.

002538 Wode-Helgodt, Birgitta. Dept. of Psychiatry, Laboratory of Experimental Psychiatry, Karolinska Institutet, Stockholm S-10401, Sweden **Clinical and biochemical effects of chlorpromazine in psychotic patients: relations to chlorpromazine concentrations in plasma and cerebrospinal fluid.** Stockholm, Sweden, Karolinska Institutet, 1977. 41 p.

To investigate relationships between clinical and central biochemical effects of chlorpromazine (CPZ) and to clarify the relationships between these effects and CPZ plasma and cerebrospinal fluid (CSF) levels, acutely admitted psychotic patients presenting with thought disorder, delusions, or auditory hallucinations were administered 200, 400 or 600mg fixed doses of CPZ in a 4 week double-blind study. CPZ reduced psychotic morbidity and final outcomes were more favorable for women than for men. Extrapyramidal symptoms occurred in a dose dependent manner. Concentrations of homovanillic acid (HVA) increased during treatment, suggesting a possible acceleration of transmitter metabolism in the nigrostriatal dopamine (DA) pathway. Plasma and CSF prolactin levels were markedly elevated during CPZ treatment. Antipsychotic effects were related to CPZ plasma and CSF concentrations, and side-effects were related to CPZ concentrations in CSF. Prolactin-like immunoreactive material levels correlated with change in morbidity and extrapyramidal side-effects. Study is seen to demonstrate the usefulness of the simultaneous analysis of clinical, biochemical and pharmacokinetic parameters for the understanding of the mechanism of action of chlorpromazine in psychotic patients. 54 references.

002539 Zielinski, Joseph John. Rutgers University, New Brunswick, NJ 08903 **A behavioral treatment of depression with alcoholics receiving pharmacological aversive conditioning. (Ph.D. dissertation).** Dissertation Abstracts International. Ann Arbor, MI, Univ. M-films, No. 77-17579 HC$15.00 MF$7.50 263 p.

The behavioral treatment of depression in alcoholics receiving pharmacological aversive conditioning is examined. Patients were 36 depressed male and female chronic alcoholics randomly assigned to one of three treatment groups receiving activity level monitoring, activity level monitoring and social skill training, or general conversation in addition to the chemical aversion treatments. Dependent measures included the rate of total abstinence at 6 months and scores on the Zang Self-Rating Depression Scale, Beck Depression Inventory, Rathus Assertiveness Schedule, MMPI, Pleasant Events Schedule and a Social Skills Assessment using simulated social situations. Subjects receiving social skill training reported feeling more socially assertive and less introverted, but behavioral measures did not confirm this apparent improvement in social skill. Subjects who received aversion treatment alone improved more than activity level monitoring plus aversion treatment subjects on several activity enjoyment level measures. Subjects maintaining abstinence for three to three and one half months reported significantly less depression, fewer physical and psychological complaints, greater enjoyment of their activities, and exhibited more socially appropriate affect in simulated social situation. Predicted inverse associations between reported

depression and reported social skill, between reported depression and subjective pleasure in activities, and the effect of situational context on assertive behaviors in simulated social interactions were all confirmed. Predicted relationships between reported depression and behavioral indices of social skill and between reported depression and activity levels were not substantiated. The overall results support the efficacy of pharmacological aversive conditioning in the treatment of chronic alcoholism, although the absence of a control group precludes a definitive interpretation of the findings. (Journal abstract modified)

12 PSYCHOTOMIMETIC EVALUATION STUDIES

002540 Bickel, P.; Dittrich, A.; Schopf, J. Psychiatrische Universitatsklinik, Forschungsdirektion, Postfach 68, CH-8029 Zurich, Switzerland **/Effects of N,N-dimethyltryptamine (DMT) on psychoticism tests./** Effekte von N,N-Dimethyltryptamin (DMT) auf Psychotizismus-Tests. Pharmakopsychiatrie/Neuro-Psychopharmakologie (Stuttgart). 10(1):10-14, 1977.

The effect of N,N-dimethyltryptamine (DMT) on Eysenck's Tests of Psychoticism was studied in 38 healthy volunteers. The 23 males and 15 females had an average age of 24.7yr. DMT, 250mg/kg dissolved in physiological saline, was given i.m. to 26 subjects and 12 subjects received saline. Test design was double-blind, and measured fluency, working, social attitudes, concentration, expressive movements, and tapping. Of the 19 variables, subjects receiving DMT differed from the controls on 7, most of these being tests of concentration. The results were similar to those of a previous trial with delta9-tetrahydrocannabinol. 17 references.

002541 Hobson, G. N.; Collis, M. L. Dept. of Psychology, University of Victoria, Victoria, B.C. V8W 2Y2 Canada **The effects of alcohol upon cooling rates of humans immersed in 7.5 degrees C water.** Canadian Journal of Physiology and Pharmacology (Ottawa). 55(3):744-746, 1977.

The effects of the ingestion of a moderate dose of alcohol, a known vasodilator, upon the cooling rate of four human subjects immersed in 7.5degrees C water for periods of time ranging from 38 to 75 min is reported. In three of the cases the cooling rate was retarded, in no case was it accelerated. This result, while lacking statistical significance, has not previously been reported. The difficulties attendant upon such research are noted. 10 references. (Author abstract)

002542 Natale, Michael; Dahlberg, Charles C.; Jaffe, Joseph. Department of Psychology, Whitely Psychology Laboratories, Franklin and Marshall College, Lancaster, PA 17604 **Effect of psychotomimetics (LSD and dextroamphetamine) on the use of primary- and secondary-process language.** Journal of Consulting and Clinical Psychology. 46(2):352-353, 1978.

The relationship between psychotomimetics and verbal language was investigated in an attempt to determine the effect of psychotomimetics (LSD and dextroamphetamine) on primary process and secondary process language. Five minute monologues were recorded for four psychoanalytic patients in LSD, dextroamphetamine, and placebo conditions. An intensive research design was adopted, and each subject was treated as an individual experiment: one patient manifested LSD induced attentuation of secondary process language; one patient showed LSD induced increase of primary process language and an increase of secondary process language when dextroamphetamine was ingested. The present findings suggest that psychotomimetics do affect ego functioning as expressed in language but that the nature of the effect (inhibition or disinhibition) is not determined by the drug alone. 4 references. (Author abstract)

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002543 Afeltowicz, Zbigniew. Klinika Chorob Psychicznych AM, 7 Debinki ul., Gdansk 80-211, Poland **/The thioridazine level in the blood serum and symptoms of the paranoid syndrome./** Poziom tiorydazyny w surowicy krwi a objawy zespolu paranoidalnego (doniesienie wstepne). Psychiatria Polska (Warszawa). 11(3):319-323, 1977.

The initial results of investigations to establish whether the thioridazine level in the blood serum may reach an optimum level at which rapid improvement of the mental state is likely to set in are presented. The thioridazine level in the blood serum was investigated in 25 patients with symptoms of the paranoid syndrome. The mental state of these patients was assessed using the Overall and Jaroszynski scale. The thioridazine level in the blood serum was found to vary from individual to individual with identical 24 hour doses and to increase only to a certain limit with increase of the doses. It is indicated that the optimum thioridazine level in the blood serum in the treatment of the paranoid syndrome can be assumed to range from 3 to 5 microgram/ml. 10 references. (Journal abstract modified)

002544 Alkana, R. L.; Parker, E. S.; Cohen, H. B.; Birch, H.; Noble, E. P. Pharmaceutical Science Center, School of Pharmacy, USC, 1985 Zonal Ave., Los Angeles, CA 90033 **Reversal of ethanol intoxication in humans: an assessment of the efficacy of L-dopa, aminophylline, and ephedrine.** Psychopharmacology (Berlin). 55(3):203-212, 1977.

The effect of pastethand treatment with L-dopa, aminophylline and/or ephedrine was investigated. In one experiment, healthy male, moderate drinkers ingested ethanol (0.8mg/kg) and then either L-dopa (1.5g) or placebo. In a second experiment, Ss ingested ethanol followed by aminophylline (200mg), ephedrine (50mg), both solutions or placebo. Treatment with L-dopa significantly reduced ethanol's effect on the EEG, motor coordination and divided attention performance. Treatment with aminophylline and/or ephedrine also significant reduced EEG and motor coordination. Findings are taken to support the hypothesis that pharmacological stimulation of central catecholamine (CA) systems may reverse some aspects of acute ethanol intoxication, and to agree with the suggestion that part of ethanol's depressant effects may be mediated via a reduction in the functional capacity of central CA systems. 67 references. (Author abstract modified)

002545 Banki, Csaba M. Dept. of Psychiatry, County Neuropsychiatric Institute, H-4321 Nagykallo 18, Hungary **Alterations of cerebrospinal fluid 5-hydroxyindoleacetic acid, and total blood serotonin content during clozapine treatment.** Psychopharmacology (Berlin). 56(2):195-198, 1978.

Cerebrospinal fluid 5-hydroxyindoleacetic acid level, and total blood serotonin content were measured in groups of manic and schizophrenic patients before and after 2, 4, 6, 10, 20, and 30 days of clozapine treatment. Cerebrospinal fluid 5-hydroxyindoleacetic acid values were elevated after 2 and 4 days and returned to baseline levels after 6 days or more. Blood serotonin content, in contrast, increased gradually and remained high even after 30 days. Neither cerebrospinal fluid 5-hydroxyindoleacetic acid nor blood 5-HT correlated with age, drug dose, or clinical effectiveness, but some relationship between these and the sedative component of the clozapine action was observed. 36 references. (Author abstract)

002546 Barash, Paul G. Department of Anesthesiology, Yale University School of Medicine, New Haven, CT **Cocaine in clinical medicine.** In: Petersen, R., Cocaine: 1977. Rockville, MD, NIDA, Research Monograph No. 13, 1977. 223 p. (p. 193-200).

A brief history of the use of cocaine in medicine is presented with emphasis on the 19th century technique of using cocaine in eye surgery. The drug is capable of causing intense vasoconstriction and local anesthesia. Indications, dosage, and adverse systemic reactions are discussed. Hospital treatment of cocaine toxicity is described. It is concluded that the successful use of cocaine requires adequate preanesthetic evaluation of the patient and adherence to the appropriate dosage schedule and the ability to handle adverse reaction but that with these safegaurds, it has an excellent record of safety. 24 references.

002547 Bjerkenstedt, L.; Eneroth, P.; Harnryd, C.; Sedvall, G. Laboratory of Experimental Psychiatry, Karolinska Institutet, S-10401 Stockholm, Sweden **Effects of melperone and thiothixene on prolactin levels in cerebrospinal fluid and plasma of psychotic women.** Archiv fur Psychiatrie und Nervenkrankheiten (Berlin). 224(4):281-293, 1977.

As part of a major investigation of the relations between clinical and biochemical effects of melperone or thiothixene in psychotic patients, a study was made of the effects of these neuroleptics on radioimmunoassayable prolactin in the cerebrospinal fluid and plasma of psychotic women. A group of 63 acutely psychotic women admitted to an emergency ward with schizophrenic symptomatology was given placebo tablets for the first few days, after which 29 received melperone and 34 were given thiothixene. Small amounts of prolactin were found in the cerebrospinal fluid of most patients before treatment, equal to about 20% of that in the plasma. Both drugs elevated cerebrospinal prolactin levels significantly, although thiothixene was more potent and longer acting in this regard. There was no marked tolerance to drug effects for either drug. Results indicate that with the doses used, thiothixene causes a more marked and longer lasting blockade of central dopamine receptors controlling prolactin release. The study also demonstrates the versatility of using prolactin analyses of cerebrospinal fluid and plasma for quantitation of biochemical effects of neuroleptic drugs on the human CNS. 28 references. (Journal abstract modified)

002548 Brunia, C. H. M. no address **Propranolol: heartrate and reflexes during a task.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):618-619, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, the effects of propranolol on human heartrate and reflexes during a physical task are described. It has been demonstrated that during the performance of a task, Achilles tendon (T) reflexes show an increase in amplitude, while simultaneously recorded Hoffman (H) reflexes do not. Heartrate increases during the same task significantly. An experiment was carried out to investigate if a rise in adrenergic activity could be an important explanation for the increase of TR amplitudes during the task. Twenty normal healthy subjects in a double-blind crossover designed experiment were given a tablet of either 40mg propranolol or placebo, half an hour before the start of the experiment. At rest and during the performance of a task heartrate, T-reflexes and H-reflexes were recorded. The increase of heartrate during the task did not show up in the propranolol session. The increase of T-reflex amplitudes, which is a common finding during the task under consideration, was larger in the propranolol session. No differences with H-reflexes were found. It is concluded that the increase of T-reflex amplitudes during the physical task is only caused by fusimotor and not by sympathetic activity. It is speculated that if the sympathetic system plays a role at all, the effect is depressive rather than facilitating. (Author abstract modified)

002549 Byck, Robert; Van Dyke, Craig. Yale University School of Medicine, Department of Pharmacology, Yale University, New Haven, CT **What are the effects of cocaine in man?** In: Petersen, R., Cocaine: 1977. Rockville, MD, NIDA, Research Monograph No. 13, 1977. 223 p. (p. 97-117).

The effects of cocaine in man are reviewed from various sources including those that are reproducible in man, clinical reports, laboratory reports that were not controlled, animal reports, single case reports from reliable sources, street knowledge, and unvarifiable myths and dogma. The effects noted are classified as local effect, systemic effects, central nervous system effect, social effects, dependence, and toxic effects. It is suggested that even for effects that are generally thought to be known, there are still important questions and that some of the supposed facts concerning cocaine will probably never be adequately demonstrated. 69 references.

002550 Cloutte, G. R.; Glass, A.; Butler, S. R. no address **The influence of caffeine on the prevalence of alpha rhythm.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):533, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, the influence of caffeine on the prevalence of alpha-rhythms is described. The hypothesis that if caffeine stimulates by acting on cortical synchrony rather than through some more subtle action on individual nerve cells, alpha prevalence should be reduced after ingestion of the drug was investigated in 16 normal right-handed subjects. Their alpha prevalence was measured from electrodes each with respect to A1 and A2 under several conditions in two recording sessions which were separated by a 5-month interval. In the first session, alpha prevalence was measured before, and 40 minutes after ingestion of 250mg of caffeine. In the second session, the same procedure was used but a placebo substituted for caffeine. Analysis of variance of changes in alpha amplitude showed that the significant interactive increase in alpha prevalence which occurred following the placebo was prevented by caffeine, which indeed caused a slight but nonsignificant fall. The effect was only present with eyes open. In both sessions, right and occipital alpha prevalence was enhanced significantly. Eye opening, as expected, reduced alpha prevalence and this effect was more intense occipitally. Calculation, which reduced alpha prevalence with eyes closed, enhanced it slightly when eyes were open. (Author abstract modified)

002551 Corsini, Giovanni U.; Onali, Pierluigi, Masala, Carmelo; Cianchetti, Carlo; Mangoni, Alfonso; Gessa, Gianluigi. Department of Mental and Nervous Diseases and Pharmacology, University of Cagliari, Cagliari, Italy **Apomorphine hydrochloride-induced improvement in Huntington's chorea.** Archives of Neurology. 35(1):27-30, 1978.

The beneficia effects brought about by apomorphine hydrochloride in Huntington's chorea were investigated. Four patients affected by Huntington's chorea with a well-defined family history of the disease were injected intramuscularly with apomorphine hydrochloride in nonemetic doses. Soon

after treatment, all patients showed a marked decrease in abnormal involuntary movements. Pretreatment with ahloperidol or supiride 30 minutes prior to apomorphine treatment, prevented the therapeutic effect of this compound. It is suggested that apomorphine-induced improvement in Huntington's chorea is mediated by the stimulation of a special kind of dopamine receptor, leading to inhibition of the activity of dopaminergic neurons. 19 references. (Author abstract modified)

002552 D'Elia, Giacomo; Hanson, L.; Raotma, Heino. Dept. of Psychiatry, Sahlgrenska sjukhuset, S-41345 Gothenburg, Sweden **L-tryptophan and 5-hydroxytryptophan in the treatment of depression: a review.** Acta Psychiatrica Scandinavica (Kobenhavn). 57(3):239-252, 1978.

A review of controlled studies of the possible antidepressant efficacy of the 5-HT precursors in l-tryptophan (L-TP) and 5-hydroxytryptophan (5-HTP) in treatment of depression is presented, and their possible value in the pharmacological treatment of depressive disorders discussed. The only studies reviewed are those in which the treatment group of depressed patients (treated with a 5-HT percursor alone or in combination with an antidepressant) was compared with a simultaneious depressed control group (to which placebo and/or antidepressants were given), or studies where intraindividual comparison was used. Trials do not provide evidence for an antidepressant effect of 5-HTP. L-TP, without interacting pharmaca, does not appear to be a well documented antidepressant. The only convincing evidence for L-TP as an antidepressant is that L-TP enhances the effect of MAOI. 62 references. (Author abstract modified)

002553 Ehrlich, Barbara E.; Diamond, Jared M. Department of Physiology, University of California at Los Angeles, Los Angeles, CA 90024 **Lithium transport across the red blood cell membrane.** Federation Proceedings. 36(3):272, 1977.

The erythrocyte membrane was used as a model system to study lithium transport, the results of which will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Lithium influx and efflux seemed to mediated by different routes. Lithium efflux can be decreased in red blood cells from healthy human donors by replacing external sodium with magnesium or by adding phloretin, whereas ouabain had a negligible effect. This supports the hypothesis of lithium extrusion by sodium countertransport. Lithium influx probably occurs through passive diffusion and active transport via Na-K ATPase. Initially, the rate of lithium influx can be reduced by ouabain or phloretin, probably as a result of lithium blockage of Na-K ATPase. At 3 to 4 hr, phloretin treated erythrocytes accumulate lithium at a greater rate than untreated cells, whereas at 24 hr, erythrocytes incubated with phloretin continue to accumulate lithium while untreated cells have reached a steady state, probably as a result of the effect of phloretin on lithium efflux. 1 reference. (Journal abstract modified)

002554 Faber, J.; Hagen, C.; Kirkegaard, C.; Lauridsen, U. Birk; Moller, S. E. Medical Dept. E, Frederiksberg Hospital, Copenhagen, Denmark **Lack of effects of L-tryptophan on basal and TRH-stimulated TSH and prolactin levels.** Psychoneuroendocrinology (Oxford). 2(4):413-415, 1977.

A study was made of the effects of L-tryptophan on basal and thyrotropin releasing hormone (TRH) stimulated serum throtropin (TSH) and prolactin levels, to evaluate the reliability of the prolactin response to TRH as an indicator of degree of depression and of probability of early relapse in endogenous depression. The experiment comprised 10 subjects whom TRH stimulation tests were performed before and at the end of the third week of oral treatment with L-tryptophan. Results suggest that long-term oral administration of L-tryptophan in conventional antidepressive doses has no effect on the serum TSH and prolactin responses to TRH. 11 references.

002555 Gerson, G. R.; Jones, R. B.; Luscombe, D. K. Pain Clinic, Royal Sussex County Hospital, Brighton, England **Studies on the concomitant use of carbamazepine and clomipramine for the relief of post-herpetic neuralgia.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):104-109, 1977.

Studies on the concomitant use of carbamazepine and clomipramine in 29 patients for the relief of postherpetic neuralgia are reported. The results demonstrate that patients who completed an 8 week course of drug therapy achieved considerable relief from the pain of postherpetic neuralgia. The relief given by the combination of carbamazepine and clomipramine was superior to that provided by transcutaneous electrical nerve stimulation and considered to offer a very effective means of treating a condition which has not previously been found to respond to traditional analgesic therapy. Using a double radioisotope derivative technique, clomipramine and desmethylclomipramine were quantitatively estimated in the plasma of six patients receiving clomipramine simultaneously with carbamazepine. It was found that this drug combination resulted in increased plasma levels of both clomipramine and its primary metabolite. 13 references. (Author abstract modified)

002556 Gram, Lars F.; Sondergaard, Ib; Christiansen, J.; Petersen, G. O.; Bech, Per. Western Psychiatric Institute and Clinic, University of Pittsburgh, 3811 O'Hara Street, Pittsburgh, PA 15261 **Steady-state kinetics of imipramine in patients.** Psychopharmacology (Berlin). 54(3):255-261, 1977.

Steady state plasma level kinetics were studied in 76 patients given imipramine (IP) 150 to 225mg/day for 2 to 5 weeks. IP was given in three divided doses at 8:00 a.m.,1:00 p.m. and 5:00 p.m. Plasma concentrations of IP and its active metabolite desipramine (DMI) were determined by quantitative in situ thin layer chromatography. The plasma levels of IP and DMI showed pronounced fluctuations throughout the day with a ratio of about two between highest and lowest level. Patients with steady state levels of IP and/or DMI below 50 microgram/l reached this within 1 week of treatment. Patients with higher steady state levels reached steady state concentrations within 2 to 3 weeks. There were some intraindividual fluctuations in plasma levels from week to week after steady state had been reached. The steady state plasma levels showed a skew distribution that became normal by logarithmic transformation. The IP/DMI ratio ranged from 0.07 to 5.5with a median value of 0.47. Compared to data from amitriptyline treated patients the IP/DMI ratios had significantly lower median value and larger variation than the corresponding plasma level ratios of amitriptyline/nortriptyline. Several statistically significant differences in steady state levels between age groups were found. 24 references. (Author abstract modified)

002557 Groom, G. V. Tenovus Institute for Cancer Research, Cardiff, Wales **A review of the relationship between endocrinopathy and depression or antidepressant drugs, with particular respect to novel theories involving the opiate receptor.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):198-201, 1977.

A review of the relationship between endocrinopathy and depression or antidepressant drugs, with particular respect to

novel theories involving the opiate receptor, is presented. It is noted that studies of hormone levels in depressed patients, both untreated and during tricyclic antidepressant therapy, have shown transient elevations of plasma prolactin after each dose but little evidence of consistent changes. Plasma levels of other pituitary dependent hormones were found to be within normal limits in a group of severely depressed patients. Recent reports have suggested changes in hormone response and in diurnal hormone levels that appear to be associated with depression and its treatment. It is suggested that these require further investigation, but perhaps the most promising field for future study concerns the role of two types of brain peptide -- the enkephalins and endorphins -- both in normal brain function and in mental disorder. 21 references. (Author abstract modified)

002558 Hanssen, T.; Heyden, T.; Sundberg, I.; Wetterberg, L.; Eneroth, P. Dept. of Psychiatry, Karolinska Institute, St. Goran's Hospital, S-11281 Stockholm, Sweden **Decrease in serum-prolactin after propranolol in schizophrenia.** Lancet (London). No.8055:101-102, 1978.

In a letter to the editor, the finding of decreased serum prolactin after use of propranolol in four schizophrenic patients is discussed. Prolactin was measured by radioimmunoassay after a drug free period of 2 weeks, on steady state doeses of propranolol, and on propranolol together with phenothiazine. Prolactine levels fell in response to propranolol, but increases sevenfold after the addition of phenothiazines in all the patients. It is suggested that propranolol may result in a central blockade of the serotonin receptor function with the decrease of the prolactin releasing factor. Addition of phenothiazine derivatives with dopamine receptor blockade seems to override this serotonin blocking effect, and the serum prolactin rises. 3 references.

002559 Hawks, Richard. Division of Research, National Institute on Drug Abuse, 11400 Rockville Pike, Rockville, MD 20857 **Cocaine: the material.** In: Petersen, R., Cocaine: 1977. Rockville, MD, NIDA, Research Monograph No. 13, 1977. 223 p. (p. 47-61).

The chemistry of cocaine and its companion alkaloids found in the leaves of the shrub erythroxylon coca is presented. The molecular structure and synthesis of cocaine is described along with its metabolic pathways. Analytic methodology including gas and thin layer chromatography and qualitative assay techniques used by forensic laboratories is also discussed. It is suggested that restrictions on the use of cocaine in the early 1900's retarded the development of information on the drug and that analytical techniques need to be advanced to make up for the dearth of basic knowledge concerning both the plant and the chemical. 38 references.

002560 Heninger, George R. Department of Psychiatry, Yale University Medical School, 34 Park St. New Haven, CT 06508 **Lithium carbonate and brain function: I. cerebral-evoked potentials, EEG, and symptom changes during lithium carbonate treatment.** Archives of General Psychiatry. 35(2):228-233, 1978.

Eighteen patients were studied with behavioral ratings and the somatosensory (SER), auditory (AER), and visual (VER) cerebral evoked response and quantified EEG before and during lithium carbonate treatment. The amplitude of early positive SER components and most AER components increased during treatment, but VER did not change; the intensity of EEG delta and theta frequencies increased, and the dominant alpha frequency slowed. Patients with an increase in symptoms on treatment had the greatest increase in EEG delta intensity, and the dominant alpha frequency slowed in patients who became more depressed. A unique and specific effect of lithium carbonate on brain function is demonstrated by the EEG slowing in patients with a normal sensorium and the change in cerebral cortical activity after transmission in the somatosensory pathway over just three synapses. 43 references. (Author abstract)

002561 Hontela, S.; Nair, N. P. V.; Rosenberg, G.; Schwartz, G.; Guyda, H. Douglas Hospital Centre, 6875 LaSalle Boulevard, Montreal, Quebec H4H 1R3, Canada **Bromocriptine: effect on serum prolactin and growth hormone in psychogeriatric hospital patients.** Journal of the American Geriatrics Society. 26(2):49-52, 1978.

The effect of bromocriptine on serum prolactin (PRL) and human growth hormone (HGH) were assessed before and three hours after oral administration in 39 hospitalized geriatric patients with organic brain syndrome. Serum PRL concentrations decreased significantly irrespective of initial values (also in the seven geriatric control subjects), but HGH levels were low in all patients and did not change during the 3 hours after administration of bromocriptine. Closer scrutiny of the HGH responses to bromocriptine in five patients and five controls showed that the serum HGH response was more variable among the patients than among the controls. The findings are discussed in relation to neuroendocrine changes associated with aging, institutional living, and mental disease. 22 references. (Author abstract modified)

002562 Horn, A. S. Department of Pharmacy, University of Groningen, Groningen, The Netherlands **The binding of inhibitors of serotonin uptake to biological receptors.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):9-13, 1977.

The binding of inhibitors of serotonin uptake to biological receptors by clomipramine and other tricyclic antidepressants is examined. It is reported that the uptake of serotonin (5-hydroxytryptamine or 5-HT) into 5-HT containing nerve endings is more potently inhibited by clomipramine than by other tricyclic antidepressants, and its antidepressant activity has been attributed to this mechanism. The molecular structures of clomipramine, related tricyclic compounds and a structurally more rigid inhibitor of 5-HT uptake (EXP-561) without antidepressant activity were studied and related to their binding at receptor sites. The findings suggest that the mode of action of clomipramine may not be limited to inhibition of 5-HT uptake. 28 references. (Author abstract modified)

002563 Huws, D.; Groom, G. V. Whitchurch Hospital, Cardiff, Wales **Luteinizing hormone-releasing hormone and thyrotropin-releasing hormone stimulation studies in patients given clomipramine or 'depot' neuroleptics.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):175-181, 1977.

A study of the effects of clomipramine and neuroleptic drugs on pituitary response to stimulation by thyrotropin releasing hormone and luteinizing hormone releasing hormone in patients and normal volunteer was conducted. In subjects given clomipramine, or one of the neuroleptics flupenthixol, fluspiriline and fluphenazine, the luteinizing hormone response was found to be normal in extent but delayed. With clomipramine the basal prolactin level tended to be raised and the prolactin response symmetrical in pattern, although in some subjects abnormal in extent. Similarity between clomipramine and the neuroleptics was again found in the stimulation studies. It is concluded that these drugs affect the hypothalamic pituitary releasing mechanism and to an extent which is variable but very marked in some subjects. 1 reference. (Author abstract modified)

002564 Itil, K. Z.; Polvan, N.; Huque, M. F.; Itil, T. M. no address **Development of an alcohol-blocker, using computer-analyzed EEG.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):552, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, the development of an alcohol blocker, using computer analyzed EEG is reported. Psychostimulant properties of lisuride hydrogen maleate (LHM), a potent migraine prophylactic with antiserotoin and antihistamine properties, were discovered based on quantitative pharmaco EEG (QPEEG) investigations. Computer EEG CEEG profile of LHM was found to be almost a mirror image of alcohol. It was predicted that LHM will block the physiological and behavioral effects of alcohol. The results of a double-blind crossover study in healthy male volunteers demonstrated that LHM, administered prior to or after alcohol ingestion, blocks or reduces the EET and behavioral changes induced by alcohol in a majority of subjects. There were marked EEG changes after alcohol, and the blocking of EEG effects by LHM presented the most behavioral effects. Whether the alcohol blocking properties of LHM can be useful in the treatment of chronic alcoholism is being studied. (Author abstract modified)

002565 Itil, M.; Akpinar, S. no address **Quantitative pharmaco-EEG with antimigraine compounds.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):552-553, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, quantitative pharmaco EEG studies with antimigraine compounds are described. Based on the observations that lisuride hydrogen maleate (LHM), an analog of LSD-25, a migraine prophylactic with potent antiserotonin and antihistamine properties, produces systematic and statistically significant effects on computer analyzed human electroencephalogram, studies were conducted with a series of antimigraine compounds. Investigations demonstrated that LHM produces EEG effects which are characterized by a decrease of very slow and very fast activities and increase of 8 to 20cps waves in the primary wave measurements, and decrease of slow and increase of fast activities in the first derivative measurements of the computer analyzed EEG. Computer EEG (CEEG) profiles of LHM showed similarities to those seen after psychostimulant compounds. Methysergide, another analog of LSD-25, produces in quality similar computer EEG changes to lisuride, indicating less potent CNS effects of this compound. Higher dosages of methysergide could not be given because of side-effects. Another antimigraine compound, pizotyline, also demonstrated similar CEEG profiles to methysergide and LHM. The quantitative changes after pizotyline were also less than those of lisuride. Cyproheptadine, a potent antihistamine and antiserotonin, did not show typical psychostimulant CEEG profiles. Quantitative pharmaco EEG studies demonstrated that the migraine prophylactic effects of LHM and, in lesser degree, methysergide may be related to their CNS effects. (Author abstract modified)

002566 Itil, T. M.; Herrman, W. M.; Huque, M. F.; Irrgang, U. no address **Quantitative pharmaco-EEG with steroidal hormones.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):552, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, quantitative pharmaco EEG investigation with steroidal hormones is described. Clinical appearances indicate that a variety of hormonal substances produce behavioral alterations. Based on the hypothesis that drugs would change human brain function, the effects of a series of hormones were studied on scalp recorded computer analyzed electroencephalogram (EEG). Using the methods of quantitative pharmaco EEG (QPEEG), the immediate CNS effects of a series of steroid hormones were established. Based on the computer EEG (CEEG) profiles, the psychotropic properties of a series of active and inactive hormones were also predicted, mesterolone, an androgen, and estradiol valerate, an estrogen, produced CEEG changes similar to those seen after imipramine and amitriptyline, respectively. Thus, antidepressant properties of these compounds were suggested. Cyproterone acetate, an antiandrogen, d-norgestrel, a potent progestational hormone, and l-norgestrel, a biologically inactive isomer of norgestrel, induced CEEG profiles similar to those seen after benzodiazepine anxiolytics. Thus, clinically anxiolytic properties of these compounds were predicted. Dexamethasone, a corticoid steroid, produced CEEG profiles similar to psychostimulant compounds. The 17-alpha and 1-beta steroid isomers of mesterolone, the anabolic methalone acetate, and the glucocorticoid flucortolone, did not produce any appreciable systematic effects on human brain function. (Author abstract modified)

002567 Jones, R. B.; Luscombe, D. K.; Groom, G. V. Welsh School of Pharmacy, UWIST, Cathays Park, Cardiff, Wales **Plasma prolactin concentrations in normal subjects and depressive patients following oral clomipramine.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):166-171, 1977.

Since there is some evidence that clomipramine may stimulate prolactin secretion, studies were conducted to see how a single oral dose of clomipramine in four volunteers and continuous clomipramine treatment in small numbers of depressed patients might affect their plasma prolactin levels as measured by radioimmunoassay. The possible relationships between clomipramine dosage, plasma concentrations of clomipramine, and plasma prolactin levels were also investigated. While 21 out of 24 (87.5%) of female subjects showed raised plasma prolactin levels at some time during clomipramine treatment, only six out of 10 (60%) of males showed this response. It is reported that higher plasma prolactin levels did not correlate with plasma levels of clomipramine or its metabolite, desmethylclomipramine, or with their combined concentrations. 28 references. (Author abstract modified)

002568 Jones, R. B.; Luscombe, D. K. Welsh School of Pharmacy, UWIST, Cathays Park, Cardiff, Wales **Plasma concentrations of clomipramine and its N-desmethyl metabolite in depressive patients following treatment with various dosage regimes of clomipramine.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):63-76, 1977.

Patients showing symptoms of depressive illness were treated for a minimum period of 28 days with one of four clomipramine dosage regimes (25mg three times daily, 75mg nightly, 10mg three times daily or 30mg nightly), and the plasma fraction of sampled blood was analyzed simultaneously for clomipramine and N-desmethylclomipramine using a double radioisotope derivative technique. Mean plasma clomipramine concentrations were of the same order in the four groups, varying from 15.0to 37.9ng/ml. The formation of an N-desmethyl metabolite was confirmed and in general the plasma levels of this metabolite were found to be greater than those of the parent compound; in contrast to clomipramine, plasma N-desmethylclomipramine levels appeared to be related

to dosage. No significant relationship was established between clinical response and plasma concentrations of clomipramine, desmethylclomipramine or a combination of both. 30 references. (Author abstract modified)

002569 Kierkegaard-Hansen, A.; Pedersen, E. B.; Darling, S.; Amdisen, A. Psychopharmacology Research Unit, Psychiatric Hospital, DK-8240 Risskov, Denmark **Plasma renin substrate during lithium treatment.** International Pharmacopsychiatry (Basel). 12(4):210-214, 1977.

Plasma renin substrate was determined in patients given lithium treatment and in a longitudinal study, renin substrate was determined in nine patients before the start of lithium treatment and at intervals during 3 months of treatment. In a transversal study, 18 patients on lithium treatment for 2 to 20 years were compared with 11 control persons. In the longitudinal study, plasma renin substrate values did not, during lithium treatment, deviate significantly from pretreatment values. In the transversal study, values in the lithium treated patients did not differ significantly from values in the control group. There were no correlations between serum lithium concentrations and plasma renin substrate values. It is indicated that plasma renin substrate remains unaffected by lithium treatment of manic-depressive patients. 6 references. (Author abstract modified)

002570 Kugler, J.; Ruther, E.; Spatz, R. no address **Time course of changes in EEG and power spectra during treatment with neuroleptics.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):471, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, time courses in changes in EEG and power spectra during treatment of psychotics with neuroleptics are described. Clinical observations of acute psychoses show the most marked effects of neuroleptics during the first 4 weeks of treatment. During this time, after a period of alteration, some biochemical and vegetative functions return to the initial level, whereas antipsychotic effects persist and EEG changes are built up continuously. In the first 2 weeks of treatment with haloperidol or clozapine, a progressive increase up to 30% in power of the 9 to 12/s and 12 to 16/s range of frequencies and a 20% decrease of the 0.5to 4/s range was found, whereas the 4 to 9/s range showed a 20% increase within the first 10 days, decreasing only to 10% thereafter. These changes may express an unspecific tranquilizing or a short lasting sedative effect, whereas other specific effects persist. After 2 weeks of clozapine treatment about 20% of EEG records showed sporadic bilateral sharp waves or bursts of sharp waves. S/W paroxysms were seen in 2%. When they appeared the patient felt subjectively well and psychopathological signs were reduced. A consistent relation with epileptic convulsive seizures could not be established. (Author abstract modified)

002571 Lacey, J. H.; Crisp, A. H.; Crutchfield, M.; Hawkins, C.; Hartmann, M. Academic Dept. of Psychiatry, St. George's Hospital Medical School, London, England **Clomipramine and sleep: a preliminary communication.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):35-40, 1977.

To determine the effects of clomipramine by intravenous infusion and its withdrawal on the electrophysiological features of sleep a double-blind study was conducted. The preliminary findings reveal complex changes that make it difficult to identify the recognized stages of sleep. Total sleep time was slightly reduced, but although clomipramine appeared to produce lighter sleep and restlessness, there was no reduction in the duration of deep sleep. REM (dream or paradoxical) sleep was, however markedly suppressed by clomipramine and altered in quality, rapid eye movements being accompanied by high muscle tension. After withdrawal of clomipramine, the duration of REM sleep tended to return towards normal levels. It was also noted that the normal surge in plasma growth hormone during the first episode of slow-wave sleep was prevented by clomipramine. 12 references. (Author abstract modified)

002572 Lacey, J. H.; Crisp, A. H.; Groom, G. V.; Seldrup, J. Academic Dept. of Psychiatry, St. George's Hospital Medical School, London, England **The impact of clomipramine and its withdrawal on some nocturnal hormone profiles -- a preliminary report.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):182-189, 1977.

To test the effect of clomipramine on certain nocturnal hormone profiles, a preliminary double-blind crossover study was conducted using 12 normal subjects. Clomipramine infusions at two dosage levels (25mg and 75mg) were given to all subjects on two successive nights; they were associated with a rapid rise in plasma cortisol levels, followed by slightly elevated levels 24 hours after withdrawal. The normal upsurge in plasma growth hormone during the first part of the night appeared to be inhibited by clomipramine infusion given at much the same time, but slow-wave sleep was unaffected. Plasma prolactin levels showed a marked rise during and after clomipramine infusion. The effects on sleep (restlessness, increased muscular tone) and on hormone levels are interpreted as arousal, possibly operating via the hypothalamic pituitary axis. 12 references. (Author abstract modified)

002573 Lake, C. Raymond; Wood, James H.; Ziegler, Michael G.; Ebert, Michael H.; Kopin, Irwin J. Laboratory of Clinical Science, NIMH, Bldg 10, Room 2D-46, Bethesda, MD 20014 **Probenecid-induced norepinephrine elevations in plasma and CSF.** Archives of General Psychiatry. 35(2):237-240, 1978.

Studies were conducted to determine the effect of probenecid on norepinephrine levels in plasma and cerebrospinal fluid in 20 neurologic patients. Increased levels of norepinephrine in plasma and cerebrospinal fluid were measured when probenecid was administered in divided oral doses totaling 100mg/kg. This technique is commonly used to measure the rate of accumulation of acidic metabolites of certain brain neurotransmitter biogenic amines in cerebrospinal fluid after blockage of their transport into blood. Since levels of 3-methoxy-4-hydroxy-phenyethyleneglycol, a neutral metabolite of norepinephrine, are also elevated after high oral doses of probenecid. It is argued that increases of cerebrospinal and plasma norepinephrine levels may be directly related to probenecid-induced release of this amine from noradrenergic neurons. 37 references. (Author abstract modified)

002574 Langer, Gerhard; Sachar, Edward J. Dept. of Psychiatry, Columbia Univ. College of Physicians and Surgeons, 722 W. 168th St., New York, NY 10032 **Dopaminergic factors in human prolactin regulation: effects of neuroleptics and dopamine.** Psychoneuroendocrinology (Oxford). 2(4):373-378, 1977.

In a study of dopaminergic factors in human prolactin regulation, the fact that plasma prolactin (PRL) concentration remained elevated above baseline for at least 7 hours following a single administration of haloperidol, is interpreted as a measure of dopaminergic blockade. With six normal men as their own controls, dose/PRL response curves of haloperidol,

prochlorperazine and thiothixene were found to be essentially parallel, suggesting a common antidopaminergic mechanism of action when releasing PRL. In two studies, dopamine hydrochloride was infused at a constant rate; the DA infusion was started either immediately after a neuroleptic had been given or 30 min later. In the first study DA totally antagonized the neuroleptic-induced PRL response; in the second study DA suppressed the neuroleptic-induced high PRL concentration to baseline level within 1 hr. These findings provide further support for the hypothesis that the PRL response to a neuroleptic is a valid test of dopaminergic blockade in man. 11 references. (Author abstract modified)

002575 Langer, Gerhard; Sachar, Edward J.; Gruen, Peter H. Dept. of Psychiatry, Columbia Univ. College of Physicians and Surgeons, New York, NY **Prolactin response to neuroleptic drugs in normal and schizophrenic subjects.** Psychopharmacology Bulletin. 14(1):8-9, 1978.

A paper read at the annual meeting of the New Clinical Drug Evaluation Units of NIMH in Key Biscayne, FL, May 1977, on prolactin (PRL) response to neuroleptic drugs in normal and schizophrenic Ss is presented. Mean peak PRL responses to chlorpromazine in normal and schizophrenic Ss were compared and found to be similar. Mean suppression of PRL baseline by L-DOPA was also similar, supporting the conclusion that hypothalamic dopaminergic activity regulating PRL in normal and schizophrenic men is similar. Maximal PRL response to doses of neuroleptics, which are subtherapeutic for most schizophrenics, appears to limit its application for a correlation with clinical response. PRL response to neuroleptics is adjudged a valid test of dopaminergic blockade in man. 8 references.

002576 Langer, Gerhard, Matussek, Norbert. Dept. of Psychiatry, College of Physicians and Surgeons of Columbia Univ., 722 W. 168th St., New York, NY 10032 **Dextro-and L-amphetamine are equipotent in releasing human growth hormone.** Psychoneuroendocrinology (Oxford). 2(4):379-382, 1977.

To investigate the regulation of human growth hormone (HGH) study comparing HGH responses to D and L amphetamine in normal subjects was conducted. Peak plasma human growth hormone (HGH) response to a single intravenous administration of D-amphetamine and L-amphetamine sulfate was evaluated in ten healthy subjects each being his own control. No statistical difference was found between the mean HGH responses of the subjects to either amphetamine isomer. Also, the number of deficient HGH responses to D-amphetamine and L-amphetamine was equal. By analogy with similar data from studies in monkeys, the involvement of noradrenergic rather than dopaminergic mechanisms in mediating amphetamine-induced HGH release in man is tentatively suggested and possible implications for recent neuroendocrinological findings in endogenous depressives are discussed. 12 references. (Author abstract)

002577 Luscombe, D. K.; Jones, R. B. Welsh School of Pharmacy, UWIST, Cathays Park, Cardiff, Wales **Effects of concomitantly administered drugs on plasma levels of clomipramine and desmethylclomipramine in depressive patients receiving clomipramine therapy.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):77-78, 1977.

To examine the effects of concomitantly administered drugs on plasma levels of clomipramine and desmethylclomipramine in depressive patients receiving clomipramine therapy, a study was conducted. In particular, steady state plasma clomipramine levels in individual patients receiving concomitant therapy with an oral contraceptive or a combination of mefenamic acid with either atropine plus diphenoxylate and nitrazepam or diazepam were found to be above the range observed in a small group of patients receiving clomipramine alone. Plasma clomipramine levels above this range were also found in two out of three patients receiving propoxyphene with paracetamol, while those in the third patient fell within it. Plasma clomipramine levels above the range observed in patients receiving clomipramine alone tended to be associated with a poor therapeutic response and more unwanted effects. Simultaneous administration of clomipramine with additional drugs is noted. (Author abstract modified)

002578 Marriott, Peter. Department of Psychiatry, St. Vincent's Hospital, Fitzroy, Victoria 3065, Australia **Tranxene.** Medical Journal of Australia (Glebe). 2(13):443, 1977.

The pharmacological qualities of the benzodiazepines and particularly clorazepate dipotassium (Tranxene) are considered in a letter. The metabolism of clorazepate and the plasma half-life of the benzodiazepines are described. Important drug interactions between anticholinergics and clorazepate are explained. A daily regime suitable for the benzodiazepines is recommended. 1 reference.

002579 Martinerie, J.; Izard, C.; Remond, A. no address **Appraisal of the effect of i.v. nicotine on the CNS.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):563-564, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, the effect of intravenously administered nicotine on the human CNS is appraised. To obtain a basic reference, both qualitative and quantitative, for a planned experimental series which should explain the stimulating or sedating nature of the smoking need, 12 subjects were given an intravenous injection of nicotine approximately equivalent to the average amount contained in one cigarette. The effects obtained with a series of different waking states, or well-defined recording conditions (rest, visual task, photic stimulation, hyperventilation, simulation of the act of smoking with an unlit cigarette, etc.)were compared, and the data were processed to find the characteristic spectral descriptions (FFT, BO HJORTH) and the mimetic analysis parameters most likely to differentiate these situations. The results provided a means to compare these states and classify them with respect to one another, depending on their activating character. (Author abstract modified)

002580 Meinck, H. M.; Kettler, D.; Mohlenhof, O. no address **Central nervous effects of the hypnotic etomidate in man.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):549-550, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, central nervous effects of the hypnotic etomidate in man are described. Doses of 0.3mg/kg etomidate were given i.v. in premedicated and non-premedicated volunteers, and the EEG, the EMG of different limb muscles, the triceps surae H-reflex, and the plantar reflex were recorded. Flashes, sound stimuli and painful pin pricks were applied additionally. About 20 seconds after starting the injection the EEG changed from alpha to delta-rhythms, superimposed often by faster low voltage waves, successively normalizing within the next 6 min. By 6 to 8 min after injection, the volunteers were awake. The EEG did not return to control activity within 15 min after injection. Myocloni or an

increase of the H-reflex was exhibited by 18 of 20 unpremedicated volunteers, being severe in three volunteers. Myocloni were enhanced markedly only by somatosensory but not by visual or acoustic stimuli. They were irregular with frequencies between 3 and 8/s and in phase only in antagonistic pairs of muscles but not in arm versus leg muscles. In contrast, strong brisk contractions could occur synchronously in all muscles recorded. The plantar reflex was increased to a generalized withdrawal reaction. Sometimes a positive Babinski sign occurred. The H-reflex amplitude increased up to 500% of control. Neither myocloni nor an increase of the H-reflex were observed in premedicated persons. Spinal mechanisms for generating the myoclonus are discussed. (Author abstract modified)

002581 Mellerup, Erling T.; Widding, Alice; Wildschiodtz, Gordon; Rafaelsen, Ole J. Psychochemistry Institute, University of Copenhagen, Righospitalet 9, Blegdamsvej, DK-2100 Copenhagen O, Denmark **Lithium effect on temperature rhythm in psychiatric patients.** Acta Pharmacologica et Toxicologica (Kobenhavn). 42(2):125-129, 1978.

The diurnal rhythm of oral temperature was studied in 55 lithium treated manic melancholic patients, 51 other psychiatric patients, and 58 healthy subjects. The lithium treated patients had a higher temperature than the normal controls during the 24 hour period and their temperature maximum was shifted towards an earlier time. When the lithium intake was postponed for 12 hours, temperature temporarily decreased to control values, but returned to the higher level after the lithium dose. The temperature results are discussed in relation to lithium-induced changes in electrolyte metabolism. 15 references. (Author abstract)

002582 Meltzer, H. Y.; Fang, V. S.; Goode, D. J. Dept. of Psychiatry & Medicine, University of Chicago, Chicago, IL **The effect of neuroleptics and alpha-methyl-p-tyrosine on serum prolactin levels in laboratory animals and man.** Psychopharmacology Bulletin. 14(1):5-7, 1978.

A paper read at the annual meeting of the New Clinical Drug Evaluation Units of NIMH in Key Biscayne, FL, May 1977, on the effect of neuroleptics and alpha-methyl-p-tyrosine on serum prolactin levels in laboratory animals and man is presented. A series of studies was undertaken to determine if the effect of antipsychotic drugs on prolactin secretion is an effective model for their action as mesolimbic or mesocortical dopamine (DA) receptors, which is believed to be relevant to their antipsychotic activity in man. Results support the hypothesis that the DA receptor which mediates the disinhibition of prolactin secretion by neuroleptics in man and rats is very similar to the DA receptor which mediates the antipsychotic action of these drugs in man. 16 references.

002583 Mohler, H.; Okada, T.; Heitz, Ph.; Ulrich, J. F. Hoffmann-La Roche & Co., Ltd., Pharmaceutical Research Dept., CH-4002 Basel, Switzerland **Biochemical identification of the site of action of benzodiazepines in human brain by 3H-diazepam binding.** Life Sciences (Oxford). 22(11):985-995, 1978.

Using postmortem human brains, a selective benzodiazepine receptor in the human brain was identified in equilibrium binding studies using 3H-diazepam as labelled ligand. Results indicate that benzodiazepines, bind in a selective, stereospecific fashion to a receptor site in human brain. Diazepam, their main representative, is bound with an apparent dissociation constant of 7nM. The potency of various benzodiazepines in displacing diazepam parallels closely their therapeutic and pharmacological potencies. The density of the receptor site varies 24 fold in human brain, with the highest level in cerebral cortex and cerebellum. The apparent affinity of the receptor site, however, is remarkably similar in 20 different brain regions. The characteristics of the benzodiazepine receptor site suggest that it represents the site of therapeutic action of the benzodiazepines in human brain. 15 references. (Author abstract modified)

002584 Mulgirigama, L. D.; Pare, C. M. B.; Turner, P.; Wadsworth, J.; Witts, D. J. Dept. of Psychological Medicine, St. Bartholomew's Hospital, London, England **Tyramine pressor responses and plasma levels during tricyclic antidepressant therapy.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):30-34, 1977.

The tyramine pressor test was used on 50 patients suffering from depressive illness in a double-blind controlled trial of maprotiline and clomipramine. Clomipramine was found to have a markedly greater effect than maprotiline in diminishing the tyramine pressor response. The usefulness of the test as a research tool was confirmed. Clinically, when plasma determinations are not available, it is suggested the tyramine pressor response may be of value in monitoring the efficacy of tricyclic antidepressant therapy, including patient compliance. 15 references. (Author abstract modified)

002585 Nagy, Adam; Hansen, Tage. Dept. II, Lillihagens Mental Hospital, S-42203 Hisings Backa 3, Sweden **The kinetics of imipramine-N-oxide in man.** Acta Pharmacologica et Toxicologia (Kobenhavn). 42(1):58-67, 1978.

The kinetics of imipramine-N-oxide was studied in five healthy volunteers. The subjects were given single doses of imipramine-N-oxide (1mg/kg) by oral, i.m. and i.v. routes. Peak plasma levels of imipramine-N-oxide was reached 1 hr after oral administration. The plasma curves following oral and i.v. administration suggested a monophasic decay with half-life ranging between 1.5to 2.5hours. Pronounced individual differences were observed in the plasma and blood concentrations of imipramine-N-oxide, imipramine, and desipramine. The systemic availability of the oral dose and i.m. injection of imipramine-N-oxide was 100% and 54%, respectively. The formation of metabolites was more extensive after i.m. injection compared with other routes of administration. The concentration of imipramine-N-oxide was lower and imipramine concentration was higher in blood cells. In 13 depressed patients tested subsequently, the concentration of imipramine and desipramine in blood was lower when they were treated with imipramine-N-oxide than during treatment with the same dose of imipramine. 20 references. (Author abstract modified)

002586 Oksenkrug, G. F. Laboratoriya psikhofarmakologii, Leningradskiy NII psikhonevrologicheskiy institut im. V. M. Bekhtereva, Leningrad, USSR /**Effect of antidepressants on the absorption of serotonin by human thrombocytes.**/ Vliyanie antidepressantov na pogloshcheniye serotonina trombotsitami cheloveka. Farmakologiya i Toksikologiya (Moskva). 40(2):146-148, 1977.

Effects of new antidepressants, already approved for clinical use, on transmembranal transport of serotonin were compared with the effects of standardized antidepressants. Compounds inhibiting serotonin absorption to a high degree were labeled "greater" antidepressants, and the others "lesser" antidepressants. On the basis of the study antidepressants may be listed in the following descending order of inhibition of serotonin absorption: chlorimipramine, imipramine, prothiadene, quipazine, amitriptylin, trausabun, imipramine N

oxide, nortriptyline, desmethylimipramine, trimipramine, noveril, ludiomyl, iprindol, tacitin, and origen. 12 references.

002587 Ridges, A. Pauline. Clinical Laboratories, Fazakerley Hospital, Liverpool, England **Second-generation antidepressants as research tools -- some preliminary findings with clomipramine and maprotiline.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):24-29, 1977.

An examination of second generation antidepressants, clomipramine and maprotiline, with quite specific fields of action is reported. Certain types of depression appear to be associated with serotonin deficiency, others with deranged catecholamine metabolism, and these types may respond differently to clomipramine and maprotiline. The preliminary findings of a double-blind controlled trial designed to test this hypothesis do not permit firm conclusions, but it is suggested that some differences are emerging and biochemical monitoring before and during antidepressant therapy appears to be a promising field for further study. 23 references. (Author abstract modified)

002588 Rosadini, G.; Fassina, G. F.; Gasparetto, B.; Sannita, W. G. no address **Quantitative EEG analysis of the putative antidepressant compound F1 6654.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):543-544, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, quantitative EEG analysis of the putative antidepressant compound F1-6654, a newly developed compound described. The EEG effects have been studied of a newly developed compound displaying antidepressant action in early open clinical studies, is described. Three groups of healthy volunteers received F1-6654 and placebo, in a Latin square design. Subjects in the first group received 100mg F1-6654; subjects in the second and third groups were given 200mg and 400mg, respectively. EEG samples were recorded prior to, and for 6 hrs after the administration of F1-6654 and placebo, with a control at the 24 hr. Blood pressure, pulse rate and reported symptoms were also recorded. EEG was quantified by power spectral analysis. The hypothesis that no spectral difference would occur between baseline condition and postdrug samples was tested by calculation of the F-test. Drug differences were tested by analysis of variance, using a three-factor repeated measurer design. Drug-induced modifications in the topographic differentiation of the EEG patterns were investigated by F-test. The results indicate that F1-6654 has a mild efficacy in modifying the EEG organization. Qualitative and quantitative differences in the EEG effects of F1-6654 exist at different doses. The differences in sensitivity of the various methods of analysis are discussed. (Author abstract modified)

002589 Rotrosen, John; Angrist, Burton; Paquin, Jeanne. Neuropsychopharmacology Research Unit, Dept. of Psychiatry, New York Univ. Medical Center, New York, NY **Neuroendocrine studies with dopamine agonists in schizophrenia.** Psychopharmacology Bulletin. 14(1):14-17, 1978.

A paper read at the annual meeting of the New Clinical Drug Evaluation Units of NIMH in Key Biscayne, FL, May 1977, on neuroendocrine studies with dopamine agonists in schizophrenia is presented. Growth hormone responses to apomorphine, a direct postsynaptic agonist, and to L-DOPA, an agonist acting through presynaptic mechanisms, were measured in 20 to 40-year-old male schizophrenics, and were found to be bimodal -- a large group of Ss showed very low apomorphine responses and a small group of Ss showed unusually high apomorphine responses. Clinically, the two schizophrenic subgroups could be distinguished by subsequent responses to neuroleptic therapy. Ss with blunted growth hormone responses ultimately showed marked clinical improvement, while Ss with exaggerated growth hormone response to apomorphine failed to show any significant clinical change with neuroleptic treatment. The diminished endocrine responsivity in many chronic schizophrenics is thought to be an effect on neuroendocrine regulatory systems of chronic neuroleptic administration. 10 references.

002590 Sachar, Edward J.; Gruen, Peter H.; Altman, Norman; Langer, Gerhard; Halpern, Frieda S.; Liefer, Marvin. New York State Psychiatric Institute, 722 W. 168th Street, New York, NY 10032 **Prolactin responses to neuroleptic drugs: an approach to the study of brain dopamine blockade in humans.** In: Usdin, E., Neuroregulators and Psychiatric Disorders. New York, Oxford University Press, 1977. 627 p. (p. 242-249).

In the proceedings of a conference on Neuroregulators and Hypotheses of Psychiatric Disorders held in Pacific Grove, California, January 13-16, 1976, the use of the prolactin (PRL) responses to neuroleptic drugs as an indicator of brain dopamine (DA) blockade in humans is advanced. The PRL response to psychotropic drugs is shown to have a high correlation with the drugs' antidopaminergic profiles and with their antipsychotic efficacy. Profiles are presented for the phenothiazine and nonphenothiazine neuroleptic drugs and lithium, diazepam, pertofrane, amitriptyline and imipramine. It is noted that the PRL response of unmedicated schizophrenics and normals are similar, indicating that the tuberoinfundibular dopamine (TIDA) pathway is uninvolved in schizophrenia, although it plays a major role in PRL secretion. The neuropharmacological properties of the TIDA system are discussed, especially as they relate to the highly anticholinergic drugs' extrapyramidal side effects and rapid development of tolerance. Measurement of PRL levels in psychiatric patients is suggested as a useful clinical application to indicate failure of the patient to adhere to the medication regimen (a major reason for relapse in psychotic outpatients). Measures of dose/response relationships, antipsychotic potency, and duration of drug action are also noted as clinical applications of the PRL response indication of DA blockade. 37 references.

002591 Sarkadi, B.; Tosteson, D. C.; Pandey, G. N.; Gunn, R. B. Department of Pharmacological and Physiological Sciences, University of Chicago, Chicago, IL 60637 **Characteristics of Li+-transport in human red cells.** Federation Proceedings. 36(3):564, 1977.

Characteristics of lithium ion transport in human red blood cells was discussed at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. In the absence of external K and Na ions, Li ion was transported by a ouabain sensitive mechanism, and this Li ion movement was competitively inhibited by external K and Na ions. Li ion efflux from red cells had no ouabain sensitive component. Neither choline ion, K ion, nor Mg ion could substitute for external Na ion in stimulating downhill or uphill Li efflux. Energy depletion of the cells by iodoacetamide with inosine only slightly decreased these Li ion movements, but phloretin and furosemide completely inhibited them. Partial inhibition could be achieved by ethacrynic acid and quinidine, but chlorobutanol did not affect Na ion stimulated Li ion movement. Ouabain insensitive lithium ion influx was stimulated by external K ion, whereas the presence of K ion was not required for Na ion dependent Li ion counterflow in either

direction. Up to 5mM intracellular Li ion did not increase the rate of the ouabain insensitive K ion movement. 1 reference. (Journal abstract modified)

002592 Scarone, S.; Giordana, F.; Rognoni, V.; Resele, L.; Lenti, C.; Ponzano, M.; Maffei, C. no address **An EEG computer analysis of chlorpromazine effects in psychotic subjects.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):535, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, an EEG computer analysis of chlorpromazine (CPZ) effects in psychotic subjects is undertaken. The EEG of psychotic subjects was studied by means of mathematical techniques of analysis after CPZ administration. To this purpose the conventional EEG of 12 subjects was examined. The EEG mathematical analysis has given these results: 1) modification of the EEG activity in all subjects; 2) increase of the low frequency bands after CPZ acute administration and recovery of the former EEG pattern after chronic administration; and 3) increase of the alpha-band after chronic administration. These results are discussed in relation to the neurophysiological and behavioral effects of the drug. (Author abstract modified)

002593 Schnee, Jack. no address **Anxiety revisited.** American Journal of Psychoanalysis. 37(4):299-307, 1977.

Clinical observations of differing reactions to various medications are related to known physiological and analytic concepts of anxiety. The psychoanalytic concepts of Freud, Rank, Horney, Sullivan, Rogers, Maslow, and Kelman are reviewed. In addition to a review of interpersonal theory, the question of whether neurotic anxiety differs qualitatively and quantitatively from psychotic anxiety is addressed. Theoretical sources of schizophrenic anxiety are examined to illustrate the psychodynamic difference between neurotic and psychotic anxiety, and neurophysiological factors are considered. It is concluded that: 1) anxiety is a holistic phenomenon; 2) different forms of anxiety may exist, distinguishable diagnostically, etiologically, and symptomatically; and 3) anxiety is an intermediate, common pathway for differing initiating factors. Tricyclic drug effects are cited to validate these conclusions. 9 references.

002594 Siegel, Ronald K. Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA **Cocaine: recreational use and intoxication.** In: Petersen, R., Cocaine: 1977. Rockville, MD, NIDA, Research Monograph No. 13, 1977. 223 p. (p. 119-136).

The discovery of cocaine, its continued use, and the consequences of that use are explored. Psychological intoxication is seen as the primary reason for the continued use of cocaine and the nature and extent of this intoxication in a group of contemporary users is described. Initial use of cocaine by humans, it is hypothesized, is the result of accidental self-administration of coca, perhaps modeled from animal use of the coca plant. Control of dosages in recreational use of the drug, it is concluded, can be effective in limiting adverse reactions but it is suggested that the effects, which are not uniformly predictable, need further study to determine the variables affecting their production. 41 references.

002595 Smith, J. A.; Mee, T. J. X.; Barnes, J. L. C. Department of Pharmaceutical Chemistry, University of Bradford, Bradford, England **Elevated melatonin serum concentrations in psychiatric patients treated with chlorpromazine.** Journal of Pharmacy and Pharmacology (London). 29(Suppl.):30p, 1977.

In a paper read at the 114th meeting of the British Pharmaceutical Conference, held in Sheffield, England, during September 1977, elevated melatonin serum concentrations in psychiatric patients treated with chlorpromazine were reported. Investigating the hypothesis that transmethylation by pineal hydroxyindole-o-methyl transferase might be implicated in the pathogenesis of abnormal mental states, a radioimmune assay was used to estimate the elevation of daytime melatonin (and possibly nighttime) serum concentrations in five psychiatric patients being treated with varying doses of chlorpromazine, and who were thus producing high concentrations with little rhythm. The daytime concentrations were enhanced four to five times over normal, while the nighttime increase was one and one half times normal. 9 references.

002596 Stahl, Stephen M.; Meltzer, Herbert Y. Department of Pharmacological and Physiological Sciences, University of Chicago, Pritzker School of Medicine, Chicago, IL 60637 **The human platelet as a model for the dopaminergic neuron: kinetic and pharmacologic properties and the role of amine storage granules.** Experimental Neurology. 59(1):1-15, 1978.

To determine if the human platelet might serve as a pharmacologic model for the study of central nervous system dopaminergic neurons in patients with diseases such as parkinsonism, Huntington's chorea, and schizophrenia, the characteristics of dopamine (DA) accumulation by human platelets were determined and compared to those of DA accumulation by central nervous system dopaminergic neurons as well as by isolated platelet amine storage granules. The accumulation of DA by human platelets was not kinetically saturable, and was not significantly inhibited by ouabain, metabolic inhibitors, or tricyclic antidepressant drugs. Serotonin did not compete for the accumulation of DA by platelets, but reserpine, tetrabenazine, and N-ethylmaleimide each inhibited platelet DA accumulation. The accumulation of DA by isolated platelet amine storage granules was similarly not saturable, was not diminished by ouabain, metabolic inhibitors, or tricyclic antidepressants, yet was inhibited by reserpine, tetrabenazine, or N-ethylmaleimide. The accumulation of DA by human platelets does not meet the requirements of a model for the high affinity, kinetically saturable uptake of DA by central nervous system dopaminergic neurons which is inhibited by ouabain and metabolic inhibitors. The data suggest that DA accumulation by human platelets is mediated via passive diffusion of dopamine into the platelet followed by binding of DA by the amine storage granules. Findings have relevance to studies of platelet dopamine uptake in parkinsonism and Huntington's chorea. 35 references. (Author abstract)

002597 Stiller, Richard L.; Marynowski, Stanley; Roizin, Leon; Perel, James M. New York State Psychiatric Institution, New York, NY 10032 **Imipramine, its N-desmethyl and hydroxy metabolites in plasma: micro determination by alkaline flame-ionization gas chromatography (AFID-GC).** Federation Proceedings. 36(3):397, 1977.

A method used for determining therapeutic concentrations of imipramine, 2-hydroxyimipramine, desipramine, and 2-hydroxydesipramine in the plasma of patients receiving 3.5mg/kg imipramine t.i.d.,was described at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. The new method involves alkaline flame ionization and gas chromatography. Amitriptyline served as an internal standard. This procedure affords the first reliable simultaneous determination for imipramine and its metabolites in a range of 5 to 1000ng/ml. Details of the procedure and retention times for imipramine and its metabolites are given. (Journal abstract modified)

002598 Stockard, J. J.; Rossiter, V. S.; Jones, T. A.; Sharbrough, F. W. no address **Effects of centrally acting drugs on brainstem auditory responses.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):550-551, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, the effects of centrally acting drugs on brainstem auditory responses are described. Because of the clinical importance of brainstem auditory evoked response (BAER) abnormalities, the potential of several clinically used drugs for producing false positive BAER abnormalities was investigated. Neither chronic nor acute diphenylhydantoin toxicity produced BAER abnormalities despite serum levels greater than 50 micrograms/ml. Therapeutic phenobarbital and ethosuximide levels also did not produce central response abnormalities (abnormalities beginning after wave I). Phenothiazines, benzodiazepines and short acting barbiturates dis not alter normal BAERs in man or cats receiving therapeutic or toxic doses, respectively. Borderline latency abnormalities of the later BAER components were seen in one case of chlorpromazine overdosage in which hypothermia (33 degrees C) developed. The paucity of pharmacologic effects on the human BAER enhances the clinical utility of the test. Preservation of BAERs, despite drug-induced electrocerebral silence and cephalic arreflexia, allows brain death to be ruled out in profound coma due to drug intoxication. (Author abstract modified)

002599 Turner, Paul; Ehsanullah, Raihana S. B. Dept. of Clinical Pharmacology, St. Bartholomew's Hospital, London, England **Clomipramine and maprotiline on human platelet uptake of 5-hydroxytryptamine and dopamine in vitro: what relevance to their antidepressive and other actions?** Postgraduate Medical Journal (Oxford). 53(Supp. 4):14-18, 1977.

Clomipramine and maprotiline, which affect the uptake of monoamines generally held to be involved in depression and their action on uptake of 5-hydroxytryptamine 5-HT), and copamine were studied in vitro in platelets from normal human subjects. Clomipramine inhibited 5-HT uptake markedly, and that of dopamine somewhat less markedly. Maprotiline did not have a significant effect on 5-HT uptake but, at a strength of 104M, did significantly inhibit dopamine uptake. It is suggested that in view of these and other findings, the monoamine theory of depression should be modified to focus attention on the monoamine receptor mechanism, rather than on the transmitter alone. 15 references. (Author abstract modified)

002600 Viswanathan, C. T.; Booker, Harold E.; Welling, Peter G. Center for Health Sciences, University of Wisconsin, Madison, WI 53706 **Bioavailability of oral and intramuscular phenobarbital.** Journal of Clinical Pharmacology. 18(2-3):100-105, 1978.

To compare the bioavailability of oral and muscular phenobarbital, the absorption of phenobarbital was compared in 5 healthy adult subjects after oral and intramuscular therapeutic doses, and serum levels of phenobarbital were determined for 21 days after dosing by means of radioimmunoassay. Serum levels were similar from both dosage routes, with peak levels occurring at 1 to 3 hours after dosing and then declining slowly with an elimination half-life of about 90 hours. The overall efficiency of phenobarbital absorption from intramuscular doses was approximately 80% of that from equivalent oral doses. Results indicated that except in cases where oral dosing is not appropriate, there is no clinical advantage in giving phenobarbital intramuscularly to adult patients. 17 references. (Author abstract modified)

002601 Willey, T. J.; Maeda, G.; Peters, M. A. no address **Primate EEG spectra before and during opioid administration.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):561, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, primate EEG spectra are compared before and during opioid administration. The experimental objective was to establish baseline drug administration effects for the opioid agonist methadone and the antagonist naloxone on the EEG. Comparisons with morphine were also undertaken. The monkey Macaca nemestrina was surgically prepared with indwelling recording probes located in autonomic/limbic brain structures and screw electrodes applied to brain surface. Spontaneous electrical activity was obtained via a multichannel PAM/FM biotelemeter. Test drugs were administered into the venous pool and continuous polygraph recordings were obtained during the uptake and elimination of the drug. Spectral time profiles were computed with a laboratory computer and plotted to reveal subtle trends associated with drug actions. Dose levels ranged from 0.25 to 4 mg/kg methadone, 1 to 16mg/kg morphine, and 0.01mg/kg naloxone. Methadone and morphine behaviorally sedated the monkey but were not equipotent. Morphine had slower onset effects and did not produce respiratory depression or seizure activity as observed with methadone at the higher doses. The EEG effects were variable and dose dependent. Alterations correlated to the drug were centered in the mesolimbic structures. These alterations were phasic before returning to predrug conditions. Naloxone administered alone did not affect the behavior or EEG activity. Drug discriminating templates applied to the EEG spectra for statistical analysis were complex. (Author abstract modified)

002602 Winsberg, Bertrand G.; Hurwic, Maria J.; Sverd, Jeffrey; Klutch, Albert. Long Island Research Institute, Health Sciences Center, T-10, Stony Brook, NY 11794 **Neurochemistry of withdrawal emergent symptoms in children.** Psychopharmacology (Berlin). 56(2):157-161, 1978.

The probenecid procedure was used to study the metabolite accumulations of dopamine (DA) and serotonin (5-HT) in the cerebrospinal fluid (CSF) of 11 children receiving chronic neuroleptic therapy. Specimens were obtained while the children were being given chronically prescribed medication (condition 1) and again 3 to 4 weeks later, following the discontinuation of drugs (condition 2). At that time, five children showed typical dyskinetic withdrawal emergent symptoms (WES) and six were free of symptoms. CSF specimens were also obtained from eight drug free children, diagnosed as having chronic organic brain disease, who served as a contrast population against which the findings were evaluated. CSF accumulations of 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) did not differentiate the drug treated children who showed WES from those who did not manifest these symptoms. A significant decrease in 5-HIAA was found in condition 2, suggesting that chronic treatment with neuroleptics may effect 5-HT metabolism in children. The contrast population was found to have lower CSF concentrations of probenecid and were consequently of little help in clarifying the nature of the 5-HIAA decrement. A number of serious deficiencies were noted regarding the use of the probenecid procedure, and it is felt that the use of spinal taps for studying neuroleptic effects on brain metabolism in children is unlikely to provide important information with regard to either CNS drug actions ot toxicity. 28 references. (Author abstract)

002603 Yarom, A.; Dvilansky, A.; Nathan, I. Soroka University Hospital, Beersheba, Israel **Effect of cannabinoids on the uptake of serotonin in human platelets.** Israel Journal of Medical Sciences (Jerusalem). 13(11):1145, 1977.

The effects of cannabinoids on serotonin uptake, reported to the 39th meeting of the Israel Physiological and Pharmacological Society in June 1977, are summarized. Cannabinoids, natural and synthetic, were used to assess their effect on (14C)serotonin uptake of washed human platelets. No inhibitory effect on uptake was found when final concentrations of less than 10-5M were used. However, increasing the concentration of the cannabinoids to 310-5M inhibited uptake significantly. The inhibition of serotonin uptake by all drugs was observed at the saturation levels of serotonin uptake. Cannabidiol was found to be more potent than delta1-tetrahydrocannabinol (THC). The dimethylheptyl derivatives of cannabidiol and THC were less effective than the parent compound. These results suggest a dissimilarity in the effects of cannabinoids on platelet serotonin uptake in comparison to platelet aggregation. (Author abstract modified)

14 MECHANISM OF ACTION: BEHAVIORAL

002604 Adams, Anthony J.; Brown, Brian; Haegerstrom-Portnoy, Gunilla; Flom, Merton C.; Jones, Reese T. School of Optometry, University of California, Berkeley, CA 94720 **Marijuana, alcohol, and combined drug effects on the time course of glare recovery.** Psychopharmacology (Berlin). 56(1):81-86, 1978.

To examine the effects of marihuana and alcohol on the time course of glare recovery, 10 male subjects were given delta9-tetrahydrocannabinol (THC) (8 or 15mg), 0.75ml/kg 95% ethanol, or .75ml/kg 95% ethanol plus 15mg THC. The time course of light adaptation after intense light exposure is significantly delayed by alcohol, marihuana, and a combined dose of alcohol and marihuana. The marihuana-induced delay in recovery is dose related. Both drugs produce delayed recovery for at least 2 hr after drug ingestion. The combined alcohol and marihuana treatment produces little more than the effect produced by either drug alone, suggesting some antagonism between the drugs -- a suggestion supported by a significantly lower blood alcohol level for the alcohol dose when combined with marihuana than when taken alone. 11 references. (Author abstract modified)

002605 Alkana, R. L.; Willingham, T. A.; Cohen, H. B.; Parker, E. S.; Noble, E. P. Department of Psychiatry and Human Behavior, University of California at Irvine, Irvine, CA 92717 **Apomorphine and amantadine: interaction with ethanol in humans.** Federation Proceedings. 36(3):331, 1977.

Effects of postethanol treatment with dopamine stimulating drugs on intoxication in humans will be reported at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977. Twelve male moderate drinkers ingested 0.8g/mg ethanol and then either 5mg apomorphine, 200mg amantadine, or placebo, in a double-blind crossover design. Treatment with apomorphine increased the effect of ethanol on divided attention performance and objective and subjective inebriation ratings without altering blood ethanol concentrations or the rate of blood ethanol decline. Apomorphine also tended to increase the effect of ethanol on neurological function. Amantadine did not alter the effect of ethanol on any measure used. Ethanol antagonism induced by catecholamine stimulating drugs appears to result from central noradrenergic rather than combined dopamine noradrenergic stimulation. Dopaminergic stimulation may have a role in mediating ethanol depression. (Journal abstract modified)

002606 Beaumanoir, A.; Potolicchio, S. J., Jr.; Nahory, A. no address **The importance of telemetric recording in the study of neuropsychological function in epilepties.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):541, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, the importance of telemetric recording in the study of neuropsychological function in epilepsy is discussed in relation to an anticonvulsant drug study with children and adolescents. It is maintained that the administration of psychometric tests during telemetry enables the clinician to study more precisely the effect of seizures and subclinical paroxysmal activity on neuropsychological performance, and also the factors involved in the inhibition or the initiation of the epileptic discharge. During a double-blind crossover study with placebo and several anticonvulsants a population of children and adolescent epileptics underwent a clinical procedure involving telemetry, psychometric testing and serum drug level determination. A comparative analysis of psychometric test scores revealed an unfavorable effect of paroxysmal activity on neuropsychological performance. These results emphasize the need to employ telemetric recording in evaluating psychological function in epileptics. (Author abstract modified)

002607 Beaver, William T.; Feise, Grace A. Dept. of Pharmacology, Georgetown University Schools of Medicine and Dentistry, 3900 Reservoir Road, N.W., Washington, DC 20007 **A comparison of the analgesic effect of intramuscular nalbuphine and morphine in patients with postoperative pain.** Journal of Pharmacology and Experimental Therapeutics. 204(2):487-496, 1978.

In a double-blind study, using patients' subjective reports as indices of analgesia, the relative potency of intramuscular nalbuphine and morphine was compared in 56 patients with postoperative pain. Results indicate that when both intensity and duration of analgesia are considered (i.e. total analgesic effect), nalbuphine (3 and 6mg or 6 and 12mg) was 0.8to 0.9times as potent as morphine (4 and 8mg). In terms of peak analgesic effect, nalbupine was 0.7to 0.8times as potent. Both time effect curves and the relative potency estimates suggest that nalbuphine has slightly longer duration of action than morphine at doses that are equianalgesic in terms of peak effect. Side-effects observed after both morphine and nalbuphine were similar to those usually observed after the administration of potent injectable analgesics to postoperative patients. No psychotomimetic reactions were observed for nalbuphine. 17 references.

002608 Bixler, Edward O.; Kales, Anthony; Soldatos, Constantin R.; Scharf, Martin B.; Kales, Joyce D. Sleep Research and Treatment Center, Pennsylvania State University, Hershey, PA 17033 **Effectiveness of temazepam with short-, intermediate-, and long-term use: sleep laboratory evaluation.** Journal of Clinical Pharmacology. 18(2-3):110-118, 1978.

The effectiveness of 30mg temazepam for inducing and maintaining sleep was evaluated in the sleep laboratory in six insomniac subjects under conditions of short, intermediate and long-term drug administration. Administration of temazepam had no effect on sleep induction. In addition, effectiveness was not demonstrated for sleep maintenance: wake time after sleep onset was not significantly decreased on any of the three drug conditions, while the number of nightly awakenings was significantly decreased on all three drug conditions. Total wake time was decreased only slightly with short-term drug administration and was similar to baseline with intermediate

and long-term use. The percent REM sleep was essentially unchanged throughout the drug administration period. Changes in slow wave sleep were consistent with findings produced by a number of benzodiazepine hypnotics. 14 references. (Author abstract)

002609 Brezinova, Vlasta; Adam, Kirstine; Chapman, Keith; Oswald, Ian; Thomson, Joan. University Department of Psychiatry, Royal Edinburgh Hospital, Morningside Park, Edinburgh EH10 5HF, Scotland **Viloxazine, sleep, and subjective feelings.** Psychopharmacology (Berlin). 55(2):121-128, 1977.

To examine the effects of viloxazine, a recently introduced antidepressant, on sleep and self-reported mood, sleep of eight healthy volunteers (mean age 55) was recorded electrophysiologically while viloxazine 200mg was taken daily for 3 weeks, preceded and followed by a week of matching blanks. The volunteers also made ratings of their feelings on visual analogue scales. Another 15 volunteers (mean age 34) took viloxazine 300mg daily for 3 weeks, preceded and followed by 3 weeks of matching blanks, and they also made daily ratings of feelings. The drug diminishes sleep duration and causes more frequent and longer transitions into wakefulness and drowsiness. Slow wave sleep decreases and stage 2 increases rapid eye movement (REM) sleep is markedly reduced, especially initially, and there is a withdrawal rebound. Viloxazine impairs subjective concentration, mood, and quality of sleep. Three volunteers, however, had striking mood elevation. The drug causes a small loss of weight, which correlates with gastrointestinal symptoms. Three older subjects experienced withdrawal vomiting and prostration. Viloxazine shares properties with imipramine and with amphetamines. 26 references. (Author abstract modified)

002610 Bunney, William E., Jr.; Post, Robert M. Adult Psychiatry Branch, NIMH, Bethesda, MD 20014 **Catecholamine agonist and receptor hypothesis of affective illness: paradoxical drug effects.** In: Usdin, E., Neuroregulators and Psychiatric Disorders. New York, Oxford University Press, 1977. 627 p. (p. 151-159).

In the proceedings of a conference on Neuroregulators and Hypotheses of Psychiatric Disorders held in Pacific Grove, California, January 13-16, 1976, some of the behavioral effects of pharmacological agents that are incompatible or paradoxical with the catecholamine (CA) agonist and receptor hypothesis of affective illness are reviewed. A pharmacological evaluation of the CA hypothesis is presented, discussing the pharmacotherapeutic action of lithium, reserpine, the phenothiazines, the butyrophenones, tricyclics, and cocaine on patients suffering from depression or mania. Data are presented which suggest that one drug can produce opposite behavioral effects in apparently identical psychopathologic states. A mechanism is suggested by which the effects of some psychoactive drugs might be amplified by alterations in neuronal receptor sensitivity. 29 references.

002611 Cahill, Mary-Carol; Belfer, Perry Lee. Department of Psychology, Graduate School of Arts and Sciences, Fordham University, Bronx, NY 10458 **Word association times, felt effects, and personality characteristics of science students given a placebo energizer.** Psychological Reports. 42(1):231-238, 1978.

Word association times, felt effects, and personality characteristics of 30 science students given a placebo energizer and 15 controls are reported. Pill subjects were informed that the pill was an energizing drug: in actuality alls pill were lactose placebos. Word association times increased from prepill to postpill testing by an equivalent amount for both pill and control groups. On a self-rating scale of felt effects, administered prepill and postpill, no difference in a perceived activation was recorded for either group. The placebo reactivity of pill subjects, defined in relation to the speed of associative production of the control group as a standard, indicated no differences among placebo reactors, antireactors, and nonreactors on any of the scales of the Personality Research Form. 11 references. (Author abstract modified)

002612 Clayton, A. B.; Harvey, P. G.; Betts, T. A. Dept. of Transportation and Environmental Planning, University of Birmingham, Birmingham B15 2TT, England **The effects of two antidepressants, imipramine and viloxazine, upon driving performance.** Psychopharmacology (Berlin). 55(1):9-12, 1977.

To determine the effects of imipramine and viloxazine on driving performance, 40 male volunteers were randomly assigned to one of four treatment groups on a doubleblind basis: 1) imipramine 25mg t.d.s.;2) viloxazine 50mg t.d.s. 3) placebo; and 4) control (no tablets). Tests were carried out before treatment, 2 hr after the first dose, on Day 3 after seven doses, and on Day 7 after 21 doses. The driving tasks consisted of weaving around a series of bollards while simultaneously responding to an auditory logic task and a gap acceptance task. Using an analysis of covariance repeated measures design, it was found that imipramine tended to increase the level of risk acceptable to the subject as compared to either placebo or control. Imipramine also impaired performance on other tasks. Viloxazine appeared to be little different from either placebo or control on any of the tasks. 16 references. (Author abstract modified)

002613 D'Elia, Giacomo; Lehmann, J.; Raotma, Heino. Dept. of Psychiatry, Sahlgrenska sjukhuset, S-41345 Gothenburg, Sweden **Influence of tryptophan on memory functions in depressive patients treated with unilateral ECT.** Acta Psychiatrica Scandinavica (Kobenhavn). 57(3):259-268, 1978.

To examine possible influences on memory from L-tryptophan (L-TP), a double-blind comparison of the anterograde dysmnesic effect after a unilateral electroconvulsive therapy (ECT) series was carried out in depressive patients randomly assigned to two treatment groups, one receiving orally administered L-TP (6g daily) and ECT, the other placebo and ECT. The groups were similar in a number of background variables and in degree of depression. Scores for three operationally defined memory variables, immediate memory (IMS), delayed memory (DMS) and forgetting (FS), were obtained before the ECT series and 4 days after, the patients being on L-TP treatment or placebo on both occasions. The results were as follows: 1) before treatment there was a higher FS in one test (30 Word-Pair Test and after treatment a higher FS in another test (30 Face Test) in the L-TP group than in the placebo group, both findings indicating an adverse influence of L-TP; 2) there were a number of correlations between serum L-TP concentration levels and memory variables, all implying a more adverse influence on memory with higher levels of L-TP. The findings suggest that L-TP has a dysmnesic effect on memory in depressive patients treated with ECT, but they need to be comfirmed before a negative influence of L-TP on memory can be considered definite. 25 references. (Author abstract)

002614 Dalby, J. Thomas; Kinsbourne, Marcel; Swanson, James M.; Sobol, Michael P. Hospital for Sick Children, 555 University Ave., Toronto, Ontario M5G 1X8, Canada **Hyperactive children's underuse of learning time: correction by stimulant treatment.** Child Development. 48(4):1448-1453, 1977.

The effects of methyphenidate (Ritalin) on hyperactive children's performance on a paired-associate learning task under three presentation rates (4, 8 and 12 see per item) were examined. The total time hypothesis states that a fixed amount of time is necessary to learn a fixed amount of material, regardless of the number of trials into which that time is divided. In a double-blind crossover design, the total time hypothesis was supported by performance in a drug state, but not by performance in a placebo state, where slower presentation rates were not utilized effectively. These results are discussed in terms of inattention in the placebo state and improved attention and use of learning time in the drug state. The methodology presented is suggested as a means of assessing attentional deficits as well as providing a diagnostic procedure for objectively evaluating the appropriateness of stimulant treatment for children referred for symptoms of hyperactivity. 18 references. (Author abstract)

002615 Ehrhardt, Anke A.; Grisanti, Gudrun C.; Meyer-Bahlburg, Heino F. L. Psychiatric Institute, Columbia, Univ., New York, NY 10032 **Prenatal exposure to medroxyprogesterone acetate (MPA) in girls.** Psychoneuroendocrinology (Oxford). 2(4):391-398, 1977.

Girls (n=15) with prenatal exogenous hormonal exposure due to maternal intake of medroxyprogesterone acetate (MPA) were compared with a closely matched control group. Studies on the long-term effects of progesterone administration during gestation have suggested that it has a mild influence on postnatal female behavior causing even greater femininity than expected in normal controls. However, it has been difficult to distinguish the effects of the prenatal hormone from those of the maternal disease state (toxemia). The results suggested that MPA was not associated with genital abnormalities in genetic females. Behavior effects of prenatal MPA appeared to be subtle and included a lower incidence of being labeled a tomboy during childhood and a more constant preference for feminine clothing styles. It is concluded that prenatal MPA may have an enhancing effect on female sexually dimorphic behavior. 10 references. (Author abstract modified)

002616 Freuchen, I.; Ostergaard, J.; Mikkelsen, B. Ohrt. Department of Anaesthesia, Svendborg Hospital, DK-5700 Svendborg, Denmark **Flunitrazepam (Rohypnol) compared with nitrazepam (Mogadon) and aprobarbital as evening premedication prior to anaesthesia: a controlled clinical trial.** Current Therapeutic Research. 23(1):90-93, 1978.

A triple-blind investigation involving 147 patients was undertaken to assess the effects of 2mg flunitrazepam, 5mg nitrazepam, and 100mg aprobarbital as oral hypnotics to ensure sleep on the evening prior to anesthesia. Flunitrazepam resulted in more rapid onset of sleep and fewer spontaneous, nocturnal awakenings (better depth of sleep) than nitrazepam and aprobarbital. Duration of sleep was identical in the three groups. A large proportion of the patients who had received flunitrazepam showed a tendency to be drowsy or sleepy or have hangovers on awakening the following morning. Flunitrazepam is considered a suitable hypnotic for use on the evening prior to anesthesia, and possesses advantages compared with nitrazepam and aprobarbital. 9 references. (Author abstract modified)

002617 Funderburk, Frank R.; Allen, Richard P.; Wagman, Althea M. I. Dept. of Psychiatry, Baltimore City Hosp., 4940 Eastern Ave., Baltimore, MD 21224 **Residual effects of ethanol and chlordiazepoxide treatments for alcohol withdrawal.** Journal of Nervous and Mental Disease. 166(3):195-203, 1978.

Recovery of sleep EEG is compared with clinical symptomatology in two treatments for alcohol withdrawal. Eighteen male alcoholics were randomly assigned to one of two alcohol detoxification treatments. One group received a low dose ethanol treatment while the other group received a chlordiazepoxide treatment. Sleep EEG and clinical measures were obtained for the final medication day and during a 6 day post-medication recovery period. The chlordiazepoxide treatment produced suppression of rapid eye movement (REM) sleep lasting for about 4 days and virtually eliminated alpha-sleep (stages III and IV) during the recovery period. The low dose ethanol treatment regimen produced less disruption of REM and alpha-sleep during the recovery period. Findings suggest that under some circumstances an ethanol treatment regimen may prove more beneficial to the healthy alcoholic patient than current regimens which employ other psychoactive medication. In particular, the long-lasting suppression of alpha-sleep during the recovery period in subjects treated with chlordiazepoxide suggests a vulnerability of the slow-wave sleep mechanisms during early alcohol abstinence and raises the possibility that this regimen prolongs functional tolerance to alcohol effects. Continued clinical evaluation of low dose ethanol detoxification treatment is suggested. 28 references. (Author abstract modified)

002618 Gabrys, Jan B. Mental Health Center, Chilliwack, B.C., Canada **Methylphenidate effect on attentional and cognitive behavior in six- through twelve-year-old males.** Perceptual and Motor Skills. 45(3, Part 2):1143-1149, 1977.

Attentional and cognitive behavior was studied in 84 learning disabled boys aged 6 through 12 years, before and during treatment with methylphenidate (Ritalin). The WISC Digit Span and Coding, identified as measures of primarily attentional behavior, showed significant improvement with methylphenidate treatment. Block design, picture arrangement, mazes, and nonverbal IQ showed significant improvement as a result of general increase in attentional behavior but the WISC Verbal IQ showed no improvement. Covariates were pretest and posttest age, parental occupational group, and length of treatment. A multivariate analysis of covariance supported the concept that methylphenidate (Ritalin) did improve performance on tests with high attentional component. Implications for the treatment of learning disabled children are discussed. 17 references. (Author abstract)

002619 Gaillard, Jean-Michel; Moneme, Ali. Clinique Psychiatrique de l'Universite de Geneve, Bel-Air, CH-1225, Chene-Bourg, Switzerland **Modification of dream content after preferential blockade of mesolimbic and mesocortical dopaminergic systems.** Journal of Psychiatric Research (Oxford). 13(4):247-256, 1977.

A study designed to test the hypothesis of a possible involvement of the mesolimbic and/or mesocortical dopaminergic systems in the emotional content of dreams in which sulpiride, a preferential blocker of dopamine receptors in these systems, was used as a tool is described. Eight normal females had their dreams collected under EEG monitoring by the awakening technique. Dream contents were rated by two judges according to nine scaled dimensions: unreality, participation of the dreamer, pleasantness, unpleasantness, verbal aggressivity, physical aggressivity, sexuality, sensoriality and time of reference in the dreamer's life. With respect to placebo condition, sulpiride decreased the number of dreams with high scores in verbal aggressivity, physical aggressivity and sexuality. This result supports the idea of a correlation between the activity of the mesolimbic and/or mesocortical

dopaminergic systems and the expression of emotions and drives in mental contents associated with REM sleep. 40 references. (Author abstract modified)

002620 Gupta, B. S.; Kaur, Surinder. Dept. of Psychology, Guru Nanak Dev. University, Amritsar, India **The effects of dextroamphetamine on kinesthetic figural aftereffects.** Psychopharmacology (Berlin). 56(2):199-204, 1978.

The effect of dextroamphetamine, primarily a central stimulant, on kinesthetic figural aftereffects (KFAEs) was examined. The subjects were selected after preliminary testing with the Eysenck Personality Inventory and were classified as extraverts, ambiverts, or introverts. d-Amphetamine was used at three dose levels and a control group was included for purposes of comparison. The 3x4 randomized block design was replicated ten times. KFAEs were measured before and after the induction experience. The results support the following conclusions: 1) neither personality grouping nor drug treatment during preinduction trials significantly affected KFAE; 2) both types of variables were, however, significantly related to behavior during the postinduction trials; 3) the extraverted subjects showed larger KFAEs than ambiverted and introverted subjects under placebo condition; 4) the extent of KFAE was reduced in extraverted and enhanced in introverted subjects under the influence of the drug; and 5) there were significant interactions between the drug treatments and personality variables in effects on KFAE. 30 references. (Author abstract)

002621 Hartley, L.; Couper-Smartt, J.; Henry, T. Dept. of Psychology, University of Leicester, Univ. Rd., Leicester LE1 7RH, England **Behavioural antagonism between chlorpromazine and noise in man.** Psychopharmacology (Berlin). 55(1):97-102, 1977.

The effects of 25mg and 75mg of chlorpromazine and of 95dBA of white noise were studied separately and together in 12 male human subjects in a visual vigilance task. Performance, analyzed by signal detection theory, showed that both noise and chlorpromazine applied separately caused impairment in similar ways. Suspended judgments were reduced and negative decisions correspondingly increased at low levels of evidence. When applied together, chlorpromazine and noise cancelled out each other's adverse effects. It is concluded that chlorpromazine is a specific behavioral antagonist of the stressful effects of noise. 21 references. (Author abstract)

002622 Hink, Robert F.; Fenton, Wayne H., Jr.; Tinklenberg, Jared R.; Pfefferbaum, Adolf; Kopell, Bert S. Department of Otolaryngology, Teikyo School of Medicine, Kaga 2-11-1, Itabashi-Ku, Tokyo 173, Japan **Vigilance and human attention under conditions of methylphenidate and secobarbital intoxication: an assessment using brain potentials.** Psychophysiology. 15(2):116-125, 1978.

To determine whether methylphenidate attenuation and secobarbital enhancement of time related performance decrements in vigilance tasks are associated with changes in selective attention or in general state, 12 subjects were treated with either 10mg of methylphenidate, 100mg of secobarbital, or a placebo in a double-blind cross-over design. Two event related potentials (N1 and P3) were measured to four tone pips presented in a random sequence. Only two of the four tones could occur in each ear. The task during the vigil was to detect a designated target tone pip. The amplitude of N1 was larger to both target and nontarget stimuli in the attended ear than to those in the unattended ear; P3 amplitude was larger only to the target stimuli. N1 amplitude decreased with time especially when secobarbital was administered. This decrement in N1 amplitude was comparable for both attended and unattended stimuli. The data support the view that the vigilance performance decrement and related drug effects on it are associated primarily with changes in general state (i.e. motivation, alertness, or arousal). 32 references. (Author abstract modified)

002623 Hrbek, Jan; Komenda, S.; Macakova, J.; Siroka, A.; Dostalova, K. Dept. of Pathological Physiology, Medical Faculty, Palacky University, Olomouc, Czechoslovakia **On the acute effect of some drugs on higher nervous activity in man followed up by the laboratory language method.** Activitas Nervosa Superior (Praha). 19(4):294-295, 1977.

A summary of a paper read at the 2nd International CIANS Congress on the acute effect of various benzodiazepine derivatives on higher nervous activity in the human language laboratory is presented. Benzodiazepine derivatives were administered to 16 student volunteers, and various learning tasks in the laboratory language method were attempted. The inhibitory effect of diazepam was noted 1 to 2 hours after administration on artificial conditioned speech reflexes established via complex tactile associations. Other drugs administered include: oxazepam, chlordiazepoxide, medazepam, and seduxen. 4 references.

002624 Komenda, S.; Hrbek, Jan; Macakova, J.; Siroka, A.; Navratil, J. Institute of Med. Physics, Palacky University, Olomouc, Czechoslovakia **Loss of information induced by reduction of data in the laboratory language method.** Activitas Nervosa Superior (Praha). 19(4):295-296, 1977.

A summary of a paper read at the 2nd International CIANS Congress on the loss of information induced by reduction of data in the laboratory language method is presented. Data concerning the performance of Ss on a paired-associate learning task following drug administration was condensed, and the information in the condensed and original data were compared. Two statistics constituted the reduced data, length of first run of incorrect responses (MO) length of first run of correct responses (ML) in the first n trials of the experiment. Use of the first statistic, MO, involves almost no loss of data, while the information in ML decreases rapidly with increasing size of n. 4 references.

002625 Kupfer, David J. Dept. of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261 **EEG sleep correlates of depression in man.** In: Hanin, I., Animal models in psychiatry and neurology. Elmsford, N.Y., Pergamon Press, 1977. 499 p. (p. 181-188).

In a paper presented at a workshop on animal models in psychiatry and neurology held in Rockville, Maryland, in June 1977, electroencephalographic (EEG) sleep correlates of depression in humans are reviewed. Major EEG sleep features identified in patients with primary depression include: 1) shortened rapid eye movement (REM) latency; 2) sleep continuity disturbances; 3) reduced slow-wave sleep (delta sleep); and 4) increased REM activity (not necessarily associated with an increased REM sleep time). Studies in humans and animals on the role of neurotransmitters in sleep regulation are reviewed. These studies suggest that cholinergic mechanisms, especially in relation to the timing of REM sleep, play an important part in the production of the EEG sleep abnormalities associated with depression. Studies of the effects of tricyclic antidepressants and monoamine oxidase inhibiting (MAOI) antidepressants on EEG sleep parameters in depressed patients are reviewed. In one study, responders to amitriptyline could be

differentiated from nonresponders on the basis of EEG sleep correlates measured after only 2 days of treatment, whereas clinical improvement was not apparent until after several weeks of therapy. Other studies have provided evidence suggesting that the effects of tricyclic antidepressants in sleep are mediated by a decrease in available acetylcholine in the brain but that MAOI do not act via a cholinergic mechanism in effecting changes in REM sleep. The implications of the reviewed material for the production of an animal model of depression is discussed. 24 references.

002626 Lahtinen, Ulla; Lahtinen, Antti; Pekkola, Pentti. Dept. of Public Health, University of Jyvaskyla, Jyvaskyla, Finland **The effect of nitrazepam on manual skill, grip strength, and reaction time with special reference to subjective evaluation of effects on sleep.** Acta Pharmacologica et Toxicologica (Kobenhavn). 42(2):130-134, 1978.

The effects of 5 and 10mg oral nitrazepam doses on manual skills, grip strength, and reaction time 8 hours after ingestion of the drugs were studied in 34 healthy female volunteers aged 19 to 22 years. The 5mg dose of nitrazepam caused a slight but insignificant decrease in psychomotor skills. With 10mg psychomotor skills were influenced significantly. Grip strength and reaction time were not influenced either by the 5 or 10mg doses. The investigations corroborate the value of the established effects of nitrazepam as a hypnotic, but recommend that caution should be exercised in prescribing the drug as a hypnotic (especially in doses exceeding 5mg) to work aged subjects as there is a risk of fatigue and significant effect on the psychomotor skills. 12 references. (Author abstract)

002627 Matejcek, M.; Devos, J. E. no address **Assessment of spontaneous and drug-induced changes in vigilance by means of a new modification of the short time spectral analysis of the EEG.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):476, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, the assessment of spontaneous and drug-induced changes in vigilance by means of a new modification of the short time spectral analysis of the EEG is described. It is maintained that carefully selected information extracted from the EEG might form a basis for a more objective evaluation of the characteristics of the mechanisms regulating vigilance and of their changes with the course of time. Some of the features of such vigilance regulating mechanisms can be significantly influenced by psychoactive drugs. Based on these considerations a technique for the investigation of changes in vigilance using quantitative EEG analysis was employed for testing drugs acting on the CNS. Drugs having so called vigilance stimulating properties would be expected to prolong the time during which the initial state of the EEG remains unchanged (resting EEG) as compared to the same under placebo conditions in a dose dependent manner; conversely sedating drugs should shorten this time. In one study, d-amphetamine was used as a stimulant and diazepam and Cloxazolam (a new benzodiazepine derivative) as sedatives. Besides the influence on the vigilance, other important parameters such as onset of drug action, maximum and duration of action, dose/response curves, equipotent doses, and specific drug effects can also be determined. (Author abstract modified)

002628 Metcalfe, J.; Olsen, G. D.; Dunham, M. J.; Krall, M. A. University of Oregon Health Science Center, Portland, OR 97201 **Effects of methadone on respiration and hemodynamics of pregnant women.** Federation Proceedings. 36(3):609, 1977.

A paper presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, Chicago, 1977, reports a study of five pregnant women on methadone maintenance at rest, during standard bicycle exercise, and throughout recovery, before and after a daily oral dose of 20 to 75mg methadone. Parameters measured or calculated were end tidal carbon dioxide partial pressure, volume of expired air, oxygen and carbon dioxide concentrations in expired air, pulse rate, arterial blood pressure, oxygen consumption, carbon dioxide production, minute ventilation, oxygen debt, oxygen cost of exercise, and alveolar ventilation at rest and during exercise. After methadone administration, end tidal CO_2 partial pressure rose at rest, during exercise, and during recovery, heartrate was lowered before and after exercise, systolic blood pressure was depressed, and alveolar ventilation during exercise was depressed. (Journal abstract modified)

002629 Miller, L. L.; McFarland, D. J.; Cornett, T. L.; Brightwell, D. R.; Wikler, A. Dept. of Psychiatry, University of Kentucky Medical Center, Lexington, KY 40506 **Marijuana: effects on free recall and subjective organization of pictures and words.** Psychopharmacology (Berlin). 55(3):257-262, 1977.

The free recall of pictures and words was compared following the administration of marihuana or placebo in a multitrial free recall task. Since pictures are thought to be registered in both visual and verbal memory stores with this encoding being mediated by some form of mental imagery, it was predicted that marihuana would produce a greater deficit in word recall in comparison to picture recall because the drug has been reported to facilitate imagery. A trend in the opposite direction followed intoxication; picture recall was inferior to word recall in the later stages of acquisition. Although overall recall was inferior under marihuana, no differences were found between the treatment conditions in subjective organization as determined by a variety of clustering measures. Recall performance following marihuana intoxication was positively related to level of recall performance in the placebo condition. 27 references. (Author abstract)

002630 Nakano, Shigeyuki; Ogawa, Nobuya; Kawazu, Yusuke; Osato, Eiko. Department of Pharmacology, Ehime School of Medicine, Ehime, Japan **Effects of antianxiety drug and personality on stress-inducing psychomotor performance test.** Journal of Clinical Pharmacology. 18(2-3):125-130, 1978.

To clarify the effects of an antianxiety drug and of personality characteristics on a psychomotor performance test, 48 healthy women college students were chosen from 64 volunteers as having either high or low levels of trait anxiety, neuroticism, or extroversion. Subjects with high trait anxiety and/or neuroticism tended to show a decrease in both speed and accuracy of the mirror drawing test (MDT) in the initial nondrug trials. Bromazepam, 5mg, a benzodiazepine derivative, decreased this decrement in highly anxious subjects but worsened the speed in less anxious subjects. The personality traits of subjects, as well as the degree to which a performance test will induce stress, must be considered when evaluating the effects of antianxiety drugs on the performance of normal volunteers. The clinical anxiety reducing efficacy of drugs may be predicted by using the MDT in subjects with high levels of anxiety and/or neuroticism. 35 references. (Author abstract)

002631 Oliveros, J. C.; Jandali, M. K.; Timsit-Berthier, M.; Remy, R.; Benghezal, A.; Audibert, A.; Moeglen, J. M. Central Dept. for Clinical Electroneurophysiology, Hospital Clinico de San Carlos, Madrid, Spain **Vasopressin in amnesia.** Lancet (London). No. 8054:42, 1978.

In a letter to the editor, the use of vasopressin in the treatment of amnesia is described in four patients. A patient with severe retrograde and anterograde amnesia, and with extensive temporal disorientation thought to be of alcoholic origin, responded symptomatically after 3 days administration, although he later developed a hypomanic condition and treatment was terminated. A patient with posttraumatic amnesia displayed improvement in long-term memory which faded after the termination of vasopressin treatment. A young man with severe retrograde amnesia stemming from a recent car accident completely recovered and maintained his memory following 7 days of treatment with vasopressin spray. The fourth patient had considerable defects in remote memory dating back to a severe car accident 6 years previous to the initiation of treatment. After vasopressin treatment he showed considerable improvement in memory, and this improvement has been maintained. These encouraging pilot studies suggest the need for a controlled trial of vasopressin in the treatment of depression. 1 reference.

002632 Paty, J.; Deliac, M. M.; Demarquez, J. L.; Brachet-Liermain, A.; Martin, Cl.; Faure, J. M. A. no address **Effects of dipropylacetate on wakefulness and sleep in human neonates.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):523, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, the effects of dipropylacetate on wakefulness and sleep in human neonates are described. Correlations between pharmacokinetic and polygraphic data in nine healthy neonates after dipropylacetate (DPA) administration are reported. Nine premature infants (conceptional age 35 weeks, 2kg weight with no neurological disturbances) were examined 21 to 31 days after birth. A single dose of 100mg/kg of DPA was given orally over the following 24 hours, in the usual conditions of life of the infant. EEG, EMG, EOG and EKG were monitored and recorded on magnetic tape. In six patients auditory and visual evoked responses were also recorded. When plasma level of DPA was higher than 100mg/l, there was a significant increase of wakefulness, and active sleep and a decrease of quiet sleep (trace alternant). These changes occurred with a delay of 6 to 12 hours after the peak of plasma DPA level. There was a recovery 15 hours later. With lower plasma levels, wakefulness and sleep changes were less marked. These changes were quantitative, they did not affect the variability of the sleep, or the cyclic organization. Delayed effects of DPA on the awakening, and the differential action upon quiet and active sleep, suggest that there is not a direct effect upon the brain, but a mediated effect, with induction of increased synthesis of neuromediators. (Author abstract modified)

002633 Pihl, R. O.; Sigal, H. Dept. of Psychology, McGill Univ., Stewart Biological Bldg., 1205 McGregor Ave., Montreal, P.Q. H3A 1B1, Canada **Motivation levels and the marihuana high.** Journal of Abnormal Psychology. 87(2):280-285, 1978.

To determine whether several different levels of motivation differentially reduce the effects of a marihuana high, 112 volunteers aged 18 to 30 were split into eight groups and two drug conditions (no drug and marihuana) and tested in one of four motivation levels: 1) simple instructions on performance; 2) instructions plus encouragement to try as hard as possible; 3) small contingent money reward; and 4) substantial contingent money reward. Time perception, choice reaction time, and a paired-associate memory task were used as dependent measures. The results indicated a significant, detrimental drug effect on all measures and a significant motivation effect on the reaction time measure. Close examination of the data suggests that the drug effect occurred because of the ineffectiveness of the motivation manipulation with the marihuana subjects. 14 references. (Author abstract modified)

002634 Raotma, Heino. Department of Psychiatry, Sahlgrenska sjukhuset, S-41345 Gothenburg, Sweden **Has tryptophan any anticonvulsive effect?** Acta Psychiatrica Scandinavica (Kobenhavn). 57(3):253-258, 1978.

To determine whether the 5-hydroxytryptamine (5-HT) precursor L-tryptophan (L-TP) exerts an inhibitory influence on epileptic seizure duration, an intraindividual crossover trial is presented in which depressed patients were treated with L-TP and unilateral electroconvulsive therapy (ECT), or with unilateral ECT alone. The oral dose of L-TP was 6g the day before ECT and 3g on the day of ECT, 4 hours before the treatment. The seizure duration was measured on EEG records. The time of the electrical stimulation needed to induce generalized seizures was similar for both treatment alternatives. Thus L-TP seems not to elevate the threshold to ECT-induced convulsions. The mean duration of a seizure was significantly shorter when the patients were treated with L-TP plus ECT than when treated with ECT alone. It is suggested that L-TP exerts an inhibitory influence on the ability to sustain epileptic activity. 12 references. (Author abstract modified)

002635 Sano, Keiji; Manaka, Shinya; Kitamura, Koichi; Kagawa, Mizuo; Takeuchi, Kazuo; Ogashiwa, Motohide; Nakamura, Norio; Ishii, Shozo; Hirai, Hideyuki. Dept. of Neurosurgery, Faculty of Medicine, University of Tokyo, Tokyo 113, Japan **Effect of CDP-choline administered intrathecally on disturbance of consciousness.** Advances in Neurological Sciences (Tokyo). 21(4):835-849, 1977.

Effects of two different types of CDP choline administration, intravenous (500mg doses, 58 cases) and intrathecal (150mg doses, 68 cases), were compared in 126 cases of patients with prolonged disturbance of consciousness. Although greater effectiveness with the intrathecal administration was confirmed, it was cautioned that convulsions might be brought on by intrathecal administration of CDP choline in preconvulsive state patients, and that its use should be limited to special cases. Thus, though safety of intrathecal administration was generally similar to that of intravenous administration, intrathecal administration was thought to be suitable only to cases where ordinary therapy is not adequate. 13 references. (Author abstract modified)

002636 Schenk, G. K.; Bente, D. no address **The alpha spectrum in schizophrenic patients due to psychopharmacological treatment and different socio-cultural settings.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):542-543, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, a study which compared the alpha spectrum in schizophrenics treated with different doses of neuroleptics in German and U.S. hospitals is described. Repeated measurements with psychiatric rating scales, psychological tests and EEG were performed. Two pretreatment EEGs were used for a reliability test. The 30 days treatment period was monitored with six EEGs per patient. The subjects were 17 patients in New York and 13 patients in Erlangen, Germany. Higher average dosages (40mg Erlangen,

90mg Manhattan), but fewer side-effects were seen in the Manhattan group. Because of artifacts only the EEGs from 15 New York patients and from nine Erlangen patients could be used for EEG analysis. Samples from 8 minutes right occipital common reference EEGs were taken and conventional analog filter analysis with 5 seconds running integration was carried out. Statistically, variance analysis and Kolmogoroff Smirnov Test were applied. The voltage levels before and after neuroleptic treatment were found to differ significantly between both groups. The time course over the entire observation period was seen to be inverse; with a parabolic time course in the Manhattan group and a V-shaped time course in the Erlangen group. After treatment the alpha peaks in both groups were shifted to the slower part of the alpha spectrum. 5 references. (Author abstract modified)

002637 Shimazono, Y.; Ando, K.; Kojima, T.; Ichise, K. no address **Eye movement, an indicator of brain function.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):498, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, eye movements are evaluated as indicators of brain functioning. The experiment was conducted to find whether there is any correspondence between eye movement pattern and fluctuation in depth of consciousness, to observe eye movement characteristics in the course of delirium tremens, and to observe eye movement changes following administration of tranquilizing drugs and hallucinogenic drugs. Horizontal eye movements during eye closure were recorded as electrooculogram with EEG, GSR and heartrate. There appeared a parallelism between the pattern of eye movement and depth impairment of consciousness. Concomitant with withdrawal of alcohol in delirium tremens patients, frequent large rapid eye movements together with slow eye movements were seen. Following administration of chlorpromazine rapid eye movements decreased, but immediately after injection of dehydrobenzperidol rapid eye movements disappeared, whereas the EEG showed no remarkable changes in the period. Hallucinogenic drugs, especially LSD25 produced peculiar patterns, i.e. rhythmic large slow pendular movements, shorter in duration than those of drowsiness, superimposed upon frequent rapid eye movements. From these observations the functional basis of rapid and slow eye movements were discussed. (Author abstract modified)

002638 Steinberg, Fred Arnold. California School of Professional Psychology, Fresno, CA **The value of the MMPI for delineating symptoms unique to positive lithium responders: a drug response and diagnostic study. (Ph.D. dissertation).** Dissertation Abstracts International. Ann Arbor, MI, Univ. M-films, No.77-21575 HC$15.00 MF$8.50 84 p.

The value of the Minnesota Multiphasic Personality Inventory (MMPI) for delineating symptoms unique to positive lithium responders was investigated on the assumption that lithium has a specific action on a specific biochemical disease process that can phenomenologically appear as different diagnostic types. Objectives were to determine how many MMPI scales would differentiate lithium responders and nonresponders, which scales would differentiate lithium non-responders and patients receiving other psychotropic medications, and whether a unique MMPI profile for lithium responders would emerge. Ss were 15 lithium responders, 15 nonresponders, and 15 patients on other psychotropic drugs. Findings indicated that the D, Pt, Ma, and Si MMPI scale scores were significantly different between lithium responders and nonresponders. Scores did not suggest a unique MMPI profile type. It is concluded that the lithium responsive syndrome does have a common symptom pattern regardless of its varying phenomenological features in different individuals. (Journal abstract modified)

002639 Timsit-Berthier, M.; Audibert, A.; Moeglen, J. M. Lab. de Neurophysiologie clinique, Dept. de Psychologie medicale & de Medecine psychosomatique, U. de Liege, Liege, Belgium /**Influence of lysine vasopressin on the EEG in man.**/ Influence de la lysine-vasopressine sur l'EEG chez l'homme. Neuropsychobiology (Basel). 4(3):129-139, 1978.

The influence of lysine vasopressin on the electroencephalogram was studied in 8 male subjects. Results indicate a dose dependent activity of lysine vasopressin on the EEG which appears to be similar to that observed in animal and man after administration of nicotine. The effect in the study subjects seems to have been independent of the action of the corticotropic hormone simultaneously released, but may have been the result of the intellectual demands made on the subjects during the testing period. 28 references. (Author abstract modified)

002640 Touyz, S. W.; Saayman, G. S.; Zabow, T. Psychology Department, University of Cape Town, Rondebosch, South Africa **A psychophysiological investigation of the long-term effects of clozapine upon sleep patterns of normal young adults.** Psychopharmacology (Berlin). 56(1):69-73, 1978.

A 25 night single-blind crossover design was employed to determine the long-term effects of clozapine on the sleep patterns of six normal young adults. Subjects received 12.50mg placebo on the first and last five nights, whereas on the intermediate 15 nights 12.5mg clozapine was administered. The subjects slept in the laboratory on the third and fourth nights to obtain baseline recordings, and on the 8th, 12th, 16th, and 20th nights to determine the effects of clozapine on sleep variables. Recordings on nights 21 and 25 were used to assess withdrawal effects. Percentage stage 1 sleep and indices of body movements during sleep were significantly reduced, suggesting that clozapine may have sleep inducing properties. There was no significant rebound of stage REM sleep during drug withdrawal despite a small but significant reduction in stage REM during drug administration. Numerous side-effects, indicative of sleepiness, were reported on the mornings following drug administration, and there was evidence of a rapid tolerance to clozapine. These findings may limit the efficacy of clozapine as an hypnotic agent over an extended period of time. Further research on insomniac subjects is therefore indicated. 15 references. (Author abstract)

002641 Veith, Jane L.; Sandman, Curt A.; George, Jack M.; Stevens, Vernon C. Dept. of Psychology, Ohio State University, Columbus, OH 43210 **Effects of MSH/ACTH 4-10 on memory, attention, and endogenous hormone levels in women.** Physiology & Behavior. 20(1):43-50, 1978.

To examine human adult female performance following treatment with the neuropeptide melanocyte stimulating hormone/adrenocorticotrophic hormone 4-10 (MSH/ACTH 4-10), young women, tested during their menstrual phase or at midcycle, received either 30mg MSH/ACTH4-10 or the saline diluent s.c. in a double-blind procedure. Behavioral testing indicated that the peptide significantly facilitated verbal memory and impaired reversal learning ability. Visual memory, field-independence, basal heartrate and state anxiety were not influenced by the treatment. Radioimmunoassays of plasma samples collected across the testing period indicated that levels of luteinizing hormone, follicle stimulating hormone, 17-beta-es-

tradiol, progesterone and cortisol were not significantly altered by the peptide. It is speculated that human sex differences in response to MSH/ACTH4-10 exist with females exhibiting an enhancement of verbal modalities. 45 references. (Author abstract modified)

002642 Volavka, Jan; Verebey, Karl; Resnick, Richard; Mule, Salvatore. Missouri Institute of Psychiatry, 5400 Arsenal Street, St. Louis, MO 63139 **Methadone dose, plasma level, and cross-tolerance to heroin in man.** Journal of Nervous and Mental Disease. 166(2):104-109, 1978.

The development of cross-tolerance between methadone and heroin was studied in postaddict volunteers who had been drug free for at least 6 weeks. Two methadone dose schedules were used; each was employed in six subjects. One schedule brought the subjects to a dose of 40mg, while the other brought them to 80mg of methadone a day. Subjects received injections of heroin (0.214mg/kg) and placebo at various times before and during methadone treatment. Subjects on both treatment schedules developed an incomplete cross-tolerance to this dose of heroin. As the dose and plasma level of methadone increased with time, the cross-tolerance to all heroin effects increased. Plasma levels did not affect the development of cross-tolerance independently of methadone dose. The most important contribution to the cross-toleance to pupillary effects was made by the duration of methadone treatment. Furthermore, the cross-tolerance to the subjective effects of heroin developed earlier than that to the pupil effect. 14 references. (Author abstract)

002643 Walters, Anne; Singh, N.; Beale, I. L. Auckland Medical School, University of Auckland, Auckland, New Zealand **Effects of lorazepam on hyperactivity in retarded children.** New Zealand Medical Journal (Dunedin). 86(600):473-475, 1977.

Seven mentally retarded children, ages 5 through 15, diagnosed as hyperactive, participated in a double-blind trial of the drug lorazepam (Ativan), a benzodiazepine derivative. Statistical analysis of behavioral records obtained from classroom observations showed that hyperactivity was greater during lorazepam dosage periods than during placebo periods. Lorazepam is therefore contraindicated for the control of hyperactivity in mentally retarded children, and might be expected to magnify management problems when used with hyperactive children. 13 references. (Author abstract modified)

002644 Wood, P. L.; Malthe-Sorenssen, D.; Cheney, D. L.; Costa E. Laboratory of Preclinical Pharmacology, NIMH, St. Elizabeths Hospital, Washington, DC 20032 **Increase of hippocampal acetylcholine turnover rate and the stretching-yawning syndrome elicited by alpha-MSH and ACTH.** Life Sciences (Oxford). 22(8):673-678, 1978.

A study was undertaken to determine whether the acetycholine (ACh) turnover rate (TRACh) of various brain areas is changed in the rat during the stretching/yawning syndrome (SYS) resulting from administration of the peptides ACTH and alpha-MSH. It was found that the stretching/yawning syndrome elicited in rats by intraventricular injection of the pituitary polypeptides, alpha-MSH and ACTH1-24, is paralleled by a twofold elevation in the hippocampal turnover rate of acetycholine (TRACh). Since the increase of TRACh is detected only in the hippocampus, it is inferred that these endogenous polypeptides particpate in the modulation of the septal/hippocampal cholinergic neurons. An interaction between alpha-MSH and ACTH with the synaptic input that regulates the septal/hippocampal cholinergic neurons is indicated by the present experiments, although they fail to document whether this interaction reflects a transsynaptic regulation. 23 references. (Author abstract)

002645 Yellin, Absalom M.; Spring, Carl; Greenberg, Lawrence M. Division of Child and Adolescent Psychiatry, Department of Psychiatry, University of Minnesota, Minneapolis, MN 55455 **Effects of imipramine and methylphenidate on behavior of hyperactive children.** Research Communications in Psychology, Psychiatry and Behavior. 3(1):15-26, 1978.

Behavior ratings were obtained from teachers and parents of hyperactive children in a double-blind crossover study comparing imipramine and methylphenidate. Both methylphenidate and imipramine were significantly more effective than placebo in reducing hyperactive behavior. However, methylphenidate was significantly more effective than imipramine. The results indicate that teachers were much more sensitive than parents to changes in hyperactive behavior and were better able to discriminate between medications. 7 references. (Author abstract)

15 TOXICOLOGY AND SIDE EFFECTS

002646 Allen, J. J.; Rack, P. H.; Vaddadi, K. S. Transcultural Psychiatry Unit, Lynfield Mount Hospital, Bradford, Yorkshire, England **Differences in the effects of clomipramine on English and Asian volunteers. Preliminary report on a pilot study.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):79-86, 1977.

To compare drug responses of members of different ethnic groups living in the same country, a pilot study of responses to clomipramine as against placebo was carried out in 20 males (11 English, nine of Indian or Pakistani origin), aged 19 to 33, all healthy, so that preexisting symptoms would not confuse assessment. While the English subjects experienced a relatively high incidence of side-effects with placebo, the Asians clearly had more severe genuine side-effects with the active drug; also their reaction times were more affected than in those of the English, and their mean peak plasma clomipramine levels following a 50mg dose were significantly lower. It is suggested that in future studies race or ethnic origin should be included as an additional named variable. 15 references. (Author abstract modified)

002647 Aschayeri, H.; Becker, W.; Bockenheimer, S. Psychiatrische und Nervenklinik, Universitat Freiburg, Hauptstrasse 5, D-7800 Freiburg, Germany /**Effects of lithium in healthy test persons.**/ Wirkung von Lithium bei gesunden Probanden im Selbstversuch. Nervenarzt (Berlin). 48(11):575-577, 1977.

The effects of 12ml to 30ml/day of lithium sulfate on the feelings and behavior of three healthy test persons are described. Sporadic physical symptoms include nausea, diarrhea, edema, tremors, dizziness, and speech disturbances; exhaustion and reduced concentration are also evident. Psychopathological symptoms, rarely reported by other authors, are loss of initiative, indifference, and limited affectivity. The symptoms begin at 0.4ml and intensify with a rise in the serum lithium level. It is cautioned that long-term lithium treatment can lead to an automaton-like existence. 30 references. (Author abstract modified)

002648 Bassuk, Ellen; Schoonover, Stephen. Beth Israel Hospital, Dept. of Psychiatry, 330 Brookline Ave., Boston, MA 02215 **Rampant dental caries in the treatment of depression.** Journal of Clinical Psychiatry. 39(2):163-165, 1978.

The etiological aspects of rampant dental caries, an occasional sidegeffect of tricyclic antidepressants and other anticholinergic drugs, are studied, with attention to the possible effects of depression and antidepressant medications on salivary properties. A typical clinical presentation of the syndrome is described and the side-effect profiles of the various tricyclic antidepressants are compared. With this clinical background, guidelines for the management of dry mouth are presented, emphasizing the importance of technical skill, safety, and continuity of care in detecting this side-effect. 13 references. (Author abstract modified)

002649 Biersner, Robert J.; Harris, Joseph A.; Ryman, D. H. Naval Submarine Medical Research Laboratory, Groton, CT 06340 **Emotional predisposition to psychotropic drug effects.** Journal of Consulting and Clinical Psychology. 45(5):943-945, 1977.

Female patients (N=107) were administered several psychological measures prior to routine dilation and curettage surgery using ketamine anesthesia to determine whether these measures were related to the psychotropic effects of ketamine. The psychological tests included measures of personality, perceived health, state/trait anxiety, and moods. The results show that moods are more highly related to the psychotropic effects of ketamine than any of the other measures. Some form of counseling intervention that would better prepare patients to cope with the surgical situation might be effective in reducing this emotionality. 7 references. (Journal abstract)

002650 Brinkmann, R.; Ebner, A. no address **Clinical value of the brainstem evoked response in coma.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):525, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, the prognostic clinical value of brainstem evoked response in comatose patients is discussed. Brainstem evoked responses (BER) were recorded in 20 patients with various depths of coma due to drug overdose (suicide attempts). Latency shifts of the most sensitive component of the BER, wave V, were found in six of the 20 patients, latencies returning to normal in four of them, when consciousness was regained. In the other two patients, the BER disappeared and both died within 48 hours. Of these six patients, five were ranked on the lowest step of the MCS, the other on the second lowest. Such patients normally receive assisted or controlled artificial respiration. Eight of the 20 patients were ranked on the lowest step of the scale, including the five patients already mentioned. Since latency shifts were not evidenced in all of these eight patients, two other mechanisms for latency shifts must therefore be taken into consideration, drug related effects and additional factors like hypoxia. 3 references. (Author abstract modified)

002651 Caine, Eric D.; Margolin, David I.; Brown, Gerald L. Sec. on Experimental Therapeutics, Lab. of Clinical Science, NIMH, 9000 Rockville Pike, Bldg. 10, Rm. 2S243, Bethesda, MD 20014 **Gilles de la Tourette's syndrome, tardive dyskinesia, and psychosis in an adolescent.** American Journal of Psychiatry. 135(2):241-242, 1978.

A case history of a 15-year-old boy suffering from Gilles de la Tourette's syndrome, characterized by multiple tics and involuntary vocalizations, who was treated with haloperidol and later developed tardive dyskinesia with a coincident psychosis is presented. On hospitalization, the patient experienced nausea and vomiting at the end of the first week after abrupt discontinuation of neuroleptic medication. The optimum treatment for this patient's drug-induced movement disorder would have been a continuation of a drug free regimen. However, this effort was contraindicated by the gradual deterioration of his mental functioning, including bizarre delusional ideation, depersonalization, auditory hallucinations, increasing disorganization, and hostility. Treatment with haloperidol was reinstituted and his abnormal involuntary movements began to diminish; his thought disorder did not remit until the dosage of haloperidol had been increased to 50mg/day. It is suggested that care be taken to differentiate symptoms of Tourette's syndrome from other childhood tics for which haloperidol or other neuroleptic treatment would not be appropriate. Evidence that tardive dyskinesia may be dose related suggests that neuroleptics be reserved for the reduction of psychotic symptoms that are the most intolerable. 6 references.

002652 Cardoni, Alex A.; Gannon, Richard H.; Stempien, Mary Jean; Petroni, Natalie C. Connecticut Poison Information Center, School of Pharmacy, University of Connecticut Health Center, Farmington, CT **Guidelines for agents used in the treatment of poisonings.** Connecticut Medicine. 42(1):38-42, 1978.

A listing of pharmacologic agents felt to be the most effective in dealing with a wide range of poisoning situations is presented. The listing is divided into eight categories including demulcents, emetics, adsorbants, lavage fluids, cathartics, diuretics, chelation, and antidotes, and recommended dosages, cautions, and contraindications are provided with each category. Amphetamines and phencyclidine overdosage should be counteracted with urine acidification, and ascorbic acid is recommended, whereas phenobarbital, lithium, and meprobamate poisoning require urine alkalization, and sodium bicarbonate is recommended. Narcotics, dextromethorphan, pentazocine and propoxyphene should be counteracted with naloxone. The antidote for ethylene glycole is ethanol. The antidote for tricyclic antidepressants is physostigmine, but this should be used only in life threatening situations. An alternative antidote for tricyclic antidepressants is phenytoin, which also serves as an antidote for phenothiazines. The need for caution when using any pharmaceutical agent is emphasized.

002653 Carroll, W. M.; Mastiglia, F. L. Neurology Service, Royal Perth Hospital, Perth, W. Australia 6000, Australia **Alpha and beta coma in drug intoxication.** British Medical Journal (London). No. 6101:1518-1519, 1977.

The occurrence of alpha and beta coma in four patients who were rendered comatose or stuperous by overdoses of nitrazepam or chlormethiazole, and in whom the EEG was dominated by frequencies in the alpha or slow beta range, is reported. The finding of diffuse or frontally predominant nonreactive alpha activity in the EEG of a patient in coma does not necessarily indicate structural brain disease, but should also suggest a possible pharmacological cause. Also, the observation of this type of EEG pattern in patients with profound drug induced coma need not imply that secondary hypoxic brain damage has occurred. The variability of the EEG changes produced by chlormethiazole when used with other drugs during alcohol withdrawal is illustrated. 5 references.

002654 Chiles, John A. Dept. of Psychiatry & Behavioral Science, University of Washington School of Medicine, RP-10, Seattle, WA 98915 **Extrapyramidal reactions in adolescents treated with high-potency antipsychotics.** American Journal of Psychiatry. 135(2):239-240, 1978.

The incidence of extrapyramidal symptoms (EPS) in psychotic adolescents secondary to the use of antipsychotic drugs (butyrophenones, thioxanthines, and piperazines) was investigated by the inpatient service at the University of Washington. For a 3 month period, all patients aged 13 to 18 who were treated for acute psychotic symptoms were closely monitored, and EPS were recorded on a rating scale. Of the 43 patients admitted over this period, 11 were started on antipsychotic medication, and all 11 had documented EPS within 48 hours of the initial dose. Given this the 100% incidence, it is suggested that brief treatment of psychotic adolescents with antiparkinsonian agents, especially in conjunction with haloperidol, prior to the administration of high potency neuroleptics may abort the development of these adverse reactions. 3 references.

002655 Coscia, C. J.; Burke, W.; Jamroz, G.; Lasala, J. M.; McFarlane, J.; Mitchell, J.; O'Toole, M. M.; Wilson, M. L. E. A. Doisy Department of Biochemistry, St. Louis University School of Medicine, St. Louis, MO 63104 **Occurrence of a new class of tetrahydroisoquinoline alkaloids in L-DOPA treated parkinsonian patients.** Nature (London). 269(5629):617-619, 1977.

The occurrence of a new class of tetrahydroisoquinoline alkaloids (TIQs) identified as norlaudanosolinecarboxylic acids (NLCAs) in the urine of Parkinsonian patients on L-DOPA with or without carbidopa treatment is reported. Comparative studies with rats on a similar regimen revealed the presence of NLCAs in brain as well as in urine. The question has been raised as to whether the efficacy of L-DOPA chemotherapy in Parkinsonism can be attributable to dopamine replacement alone. TIQs have been proposed as possible therapeutic agents, whereas some investigators have postulated that they may cause side-effects, such as the on/off phenomena observed clinically in L-DOPA chemotherapy. These hypotheses imply interaction of TIQs with catecholaminergic receptors, and evidence exists for transmitter-like behavior of simple aldehyde derived TIQs. The occurrence of NCLAs in mammalian urine and brain provides a basis for further investigation of theories concerning the role of TIQs in Parkinsonian chemotherapy. 12 references.

002656 Crome, Peter; Hampel, G.; Vale, J. A.; Volans, Glyn N.; Widdop, B.; Goulding, Roy. Poisons Unit, Guy's Hospital, London SE1, England **Haemoperfusion in treatment of drug intoxication.** British Medical Journal (London). No. 6106:174, 1978.

In a letter to the editor, a previous report of the application of XAD-4 resin hemoperfusion in the treatment of drug intoxication is questioned on the grounds that the amount of the drug removed was not sufficient to cause the clinical improvement described. The resin column and three charcoal based devices are compared. It is emphasized that the choice of hemoperfusion therapy should be based not only on clinical criteria, but also on the feasibility of removing a significant proportion of the ingested drug by efficient clearance of the blood. 5 references.

002657 Czarniawy, Aleksander; Henneberg, Maria. ul. Debowa 3, 85-626 Bydgoszcz, Poland **/Acute poisonings due to drugs in the Polish province of Olsztyn from 1971 to 1974./** Zatrucia ostre lekami w B. Wojewodztwie Olsztynskim w latach 1971-1974. Zdrowie Publiczne (Warszawa). 88(4):225-235, 1977.

A study of the epidemiology of acute drug poisoning in the city of Olsztyn and in the former county of Gizycko, Poland between 1971 and 1974 is presented. Data were obtained from ambulance service stations in Olsztyn and Gizycko, and from the County Hospital in Gizycko. The most frequent agents used in acute drug poisoning were tranquilizers (24.5%), followed by analgesics (18.6%), and barbiturates (10.8%). Suicidal poisoning prevailed at about 80% and of these adolescents and young adults accounted for 50% of all cases in the county of Gizycko, and 70% of all cases in Olsztyn. Seventy percent of all poisonings involved women. A strong control over drug distribution, and drug education are recommended. 23 references. (Journal abstract modified)

002658 Davis, J. M.; Casper, Regina. University of Chicago, Pritzker School of Medicine, Chicago, IL **Antipsychotic drugs: clinical pharmacology and therapeutic use. Part II.** Current Therapeutics (Seaforth, Australia) 18(10):129, 131, 133, 135-136, 139, 141, 143, 145-146, 1977.

The clinical pharmacology and therapeutic use of antipsychotic drugs is considered. The examination of side-effects is emphasized: autonomic, cardiovascular, allergenic, extrapyramidal, nonextrapyramidal central nervous system, long-term skin and eye, and endocrine. In addition, drug treatment is compared with psychological and social treatment. Several conclusions drawn from research on the use of drugs and psychotherapy in schizophrenia which are cited include: no evidence that antipsychotic medications are detrimental to the course of treatment; evidence that antipsychotics are effective in the treatment of schizophrenia; and evidence that patients who are denied drug treatment during initial hospitalization for a period of 6 months to 1 year do not do as well in the ensuing 3 to 5 year period as those who were initially treated with drugs.

002659 Diehl, L. W.; Herha, J. Bezirkskrankenhaus, D-8950 Kaufbeuren, Germany **/The problem of prenatal damage from long-term antiepileptic drug treatment./** Ein Beitrag zum Problem pranataler Schadigungen bei antiepileptischer Langzeitmedikation. Nervenarzt (Berlin). 48(11):608-611, 1977.

To assess the possible teratogenic effects and typical malformation syndromes of certain antiepileptic drugs and to make safe treatment possible, the case of a 26-year-old mother of three who suffered from grand mal and psychomotor attacks is discussed. The patient was treated with antiepileptic drugs from 1965 on and continuously with Tegretal (2000mg/day) and Zentropil (300mg/day) from 1967 on. She produced three normal children. No birth defects of the kinds reported in previous literature for some antiepileptic drugs occurred in any of the children. It is concluded that in keeping with previous findings 2-n-propylvalerianic acid, especially carbamezepin, is least teratogenic of the antiepileptic drugs and that prenatal damage probably depends on the combination of drugs used and the serum concentration level of the drugs. 15 references. (Author abstract modified)

002660 Extein, Irl. Clinical Psychobiology Branch, NIMH, Bldg 10, Rm. 4S239, 9000 Rockville Pike, Behtesda, MD 20014 **Methylphenidate-induced choreoathetosis.** American Journal of Psychiatry. 135(2):252-253, 1978.

The emergency room treatment with cholinomimetic and dopamine blocking medications of a patient suffering from choreoathetosis induced by methylphenidate is reported with emphasis of the role of dopaminergic and cholinergic neuronal pathways in choreiform movement disorders. The patient, a 55-year-old woman, had a long history of treatment for manic-depressive illness. Initially she was administered physostigmine to control choreoathetosis but showed no improvement

and became nauseated. She was then given haloperidol, after which she went to sleep briefly and awoke markedly improved. She was instructed to take low doses of oral haloperidol for several days, and at a 1 month followup showed no recurrence of the choreoathetosis. This response in a patient of a choreiform syndrome that was precipitated by a potentiator of dopamine and was responsive to a blocker of central dopamine receptors, is consistent with hypotheses that choreiform movement disorders involve increased dopaminergic neuronal influence in the brain. 5 references.

002661 Fann, William E.; Shannon, Ira L. Psychiatric Service, VA Hospital, Houston, TX 77211 **A treatment for dry mouth in psychiatric patients.** American Journal of Psychiatry. 135(2):251-252, 1978.

The use of a salivary substitute solution known as VA-OraLube for treating xerostomia (dry mouth) a side-effect of many major tranquilizers and tricyclic antidepressants, is described. Use of VA-OraLube as a therapeutic mouthwash to relieve the painful soft tissue problem caused by xerostomia and remineralize tooth surfaces that have been damaged as result of salivary deprivation was successful in a clinical trial of 30 psychiatric patients. VA-OraLube contains potassium phosphates, chlorides of potassium, sodium, magnesium, calcium, sodium fluoride, sorbitol, binder, flavor, dye, preservative, and water. Tests show relief of symptoms of dryness were immediate and complete. It is concluded that VA-OraLube is a safe, noninvasive, nonsystemic treatment for patients who suffer from xerostomia secondary to the administration of psychotropic drugs. 6 references.

002662 Faulkner, Thomas P.; McGinity, James W.; Hayden, James H.; Martinez, Maria; Comstock, Eric G. School of Pharmacy, Texas Southern University, Houston, TX 77004 **Pharmacokinetic studies on tolerance to sedative-hypnotics in a poly-drug abuse population: I. secobarbital.** Clinical Pharmacology and Therapeutics. 23(1):36-46, 1978.

To determine the nature and degree of tolerance to secobarbital among drug abusers, patients from a polydrug abuse treatment program with a history of sedative hypnotic abuse were titrated with secobarbital, their alleged drug of choice, to a minimal state of toxicity consisting of nystagmus, drowsiness, ataxia, and slurred speech, and blood level determinations were made, and several pharmacokinetic parameters were estimated. The patients tolerated a titration dose which was slightly, but significantly, higher than that tolerated by the control group. Cellular tolerance could be demonstrated in terms of higher blood levels determined at 7 hr after the last dose but not at the onset of toxicity. A significantly greater beta-phase disposition constant and significantly smaller area under the curve per dose in the patient population suggested the contribution of drug disposition tolerance. Statistical comparisons of these parameters were made between several subgroups of the patient population. The patients indicating a higher frequency of sedative abuse did not differ from their patient counterparts. Those patients presenting with positive screens for barbiturates on admission provided similar results except for an apparently higher volume of distribution. Patients indicating concurrent alcohol use did not differ from the overall patient population; those also using amphetamines showed no sign of tolerance or increased elimination and were indistinguishable from control subjects. 39 references. (Author abstract modified)

002663 Fruensgaard, K. Odense University Hospital, DK-5000 Odense, Denmark **Withdrawal psychosis after drugs.** Journal of Continuing Education in Psychiatry. 38(2):42-43, 1978.

To examine withdrawal psychosis 25 patients suffering psychosis following withdrawal from benzodiazepines or barbiturates were studied over a 4 1/2 year period. Typically, predelirium treatment was either omitted or was ineffective in the form of neuroleptics. In the psychotic phase, approximately half of the patients received treatment with neuroleptics which proved to be ineffective. Withdrawal psychoses may commence or become manifest as late as 12 to 14 days into the withdrawal phase, particularly after benzodiazepines. Further, sudden withdrawal of benzodiazepines in "therapeutic" doses may cause withdrawal psychoses in some patients if these drugs (or corresponding preparations) have been consumed for several years. (Journal abstract modified)

002664 Gelenberg, Alan J. Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114 **Amantadine in the treatment of benztropine-refractory extrapyramidal disorders induced by antipsychotic drugs.** Current Therapeutic Research. 23(3):375-380, 1978.

To identify patients differentially responsive to amantadine, 14 schizophrenic patients whose extrapyramidal reactions were refractory to benztropine were treated with amantadine. Antipsychotic drugs involved were high potency agents, and extrapyramidal signs were marked by severe bradykinesia, often with catalepsy. Two patients had akathisia in addition to parkinsonian signs, and one patient had akathisia alone. Six patients showed marked improvement within the first two days at 200mg of amantadine daily, while six others improved following increase to 300mg daily. One patient with parkinsonian signs plus akathisia was only minimally improved; the patient with akathisia alone became slightly worse. Amantadine has a different mode of action from benztropine, acting as a dopamine agonist; it may have special usefulness in some cases of severe drug induced parkinsonism. 23 references. (Author abstract modified)

002665 Gerlach, Jes; Rye, T.; Kristjansen, P. Sct. Hans Hospital, Psychopharmacological Research Lab., DK-4000 Roskilde, Denmark **Effect of baclofen on tardive dyskinesia.** Psychopharmacology (Berlin). 56(2):145-151, 1978.

Eighteen chronic psychiatric patients with neuroleptic induced tardive dyskinesia of one half to 9 years duration participated in a double-blind crossover study on the effect and side-effects of baclofen and placebo in the treatment of tardive dyskinesia. Each treatment phase lasted 3 weeks. Evaluation of the results included an assessment of videotape recording. Baclofen (20 to 120mg daily) reduced the hyperkinesias and increased the parkinsonism. The effect on the oral movement pattern of tardive dyskinesia was characterized by a reduced frequency, an unchanged or slightly reduced amplitude, and an increased duration of each separate mouth opening and tongue protrusion, a response pattern very similar to the response pattern of alpha-methyl-p-tyrosine, an inhibitor of the catecholamine synthesis. Sedation, muscular weakness, and confusion were observed in 50% of the patients. These side-effects, appearing mainly in elderly patients, sometimes set in before the antihyperkinetic effect, thus limiting the practical usefulness of baclofen in the treatment of tardive dyskinesia. 31 references. (Author abstract modified)

002666 Gitlin, Michael; Rosenblatt, Michael. Department of Psychiatry, UCLA, 760 Westwood Plaza, Los Angeles, CA 90024 **Possible withdrawal from endogenous opiates in schizophrenics.** American Journal of Psychiatry. 135(3):377-378, 1978.

To determine if oral naltrexone in psychotic patients, naltrexone (50 to 100mg/day p.o.)was administered for 2 weeks to three patients, two men with diagnoses of chronic schizophrenia and one woman with schizoaffective illness, depressed type. No therapeutic effect was demonstrated. Both chronic schizophrenics complained of side-effects: one of nausea, vomiting, abdominal pain, and sleepiness; and the other of headache, chills, nausea, restlessness, malaise, and shakiness. Neither patient had had a reaction to placebo administered the previous day. The persistence of the effects after drug discontinuation was seen to correlate with observed length of the opiate antagonistic action of naltrexone. Questions are raised about the role of these opiates in psychiatric disorders because of the possibility of a withdrawal syndrome. 9 references.

002667 Goncalves, N.; Gruneberg, F. Psychiatrische Klinik, Freie Universitat Berlin, Nussbaumallee 36, D-1000 Berlin 19, Germany **/Clinical laboratory studies with special regard to hepatic metabolism in schizophrenics on outpatient long-term neuroleptic medication./** Laborklinische Untersuchungen unter besonderer Berucksichtigung des Leberstoffwechsels bei Schizophrenen unter ambulanter neuroleptischer Lyngzeitmedikation. Pharmakopsychiatrie/Neuro-Psychopharmakologie (Stuttgart). 10(1):36-40, 1977.

Liver function tests were made of 68 schizophrenic outpatients treated with major tranquilizers for 3 to 18 yr. The 20 men and 48 women were 20 to 79 years old. Fifty of the patients had been under phenothiazine treatment for 15 yr or more. Some 40 of the patients were receiving perazine, 14 received clozapine, and 14 received other drugs. Laboratory tests included erythrocyte sedimentation rate, alpha-1-glycoprotein, ceruloplasmin, fibrinogen, serum glutamic pyruvic transaminase, serum glutamic oxalacetic transaminase, gamma-glutamyl transferase, total protein, serum protein electrophoresis, and glucose tolerance. Sedimentation rate was elevated in 44% of the patients. Nine patients had a decreased alpha-1-glycoprotein and ten patients showed increased fibrinogen. There was a positive correlation between prolonged sedimentation values and increased fibrinogen. Gamma-glutamyl transferase was elevated in 22 patients, and nine of these patients had an elevated SGPT or SGOT. Serum glutamic pyruvic transaminase and/or oxalacetic transaminase was elevated in 12 Pp and these two values were positively correlated. The glucose tolerance test was abnormal in 18 patients. The other liver function tests were generally normal. Some 46% of the patients (including 67% of those with abnormal glucose tolerance tests) were more than 10kg overweight. Results may be interpreted as being due to a slightly fatty liver. 25 references.

002668 Granacher, Robert P., Jr. University of Kentucky College of Medicine, Lexington, KY 40506 **The tardive dyskinesia syndrome.** Journal of the Kentucky Medical Association. 76(1):13-17, 1978.

The clinical features, epidemiology, and management of tardive dyskinesia are discussed with particular reference to the need for physicians to recognize the syndrome. Tardive dyskinesia is a hyperkinetic movement disorder seen following the prolonged use of antipsychotic drugs. The differential diagnosis of this syndrome is presented, and drugs which may suppress, modify, or exacerbate movements are discussed. Management guidelines are offered. 20 references. (Journal abstract modified)

002669 Granoff, Abbot L.; Davis, John M. Hearst & Fischer Psychiatric Associates, Ltd., Pembroke 5, Suite 331, Virginia Beach, VA 23462 **Heat illness syndrome and lithium intoxication.** Journal of Clinical Psychiatry. 39(2):103-107, 1978.

The possibility of a relationship between heat illness syndrome and lithium intoxication is discussed with reference to similarities in the symptoms, predisposing factors, and physiology of both conditions. Sodium, which is chemically similar to lithium, seems to be involved in heat illness syndrome and lithium intoxication. Heat illness syndrome, which may consist of any of 14 primary disorders, seems to affect the central nervous system with widely variable nonspecific neurological and neuromuscular signs and symptoms, similar to those brought on by lithium toxicity. It is speculated that there is a common underlying physiological mechanism to account for this similarity in symptoms. 39 references.

002670 Grant, Igor; Adams, Kenneth M.; Carlin, Albert S.; Rennick, Phillip M.; Judd, Lewis L.; Schooff, Kenneth; Reed, Robert. University of California at San Diego, School of Medicine, La Jolla, CA 92093 **Organic impairment in polydrug users: risk factors.** American Journal of Psychiatry. 135(2):178-184, 1977.

In a national collaborative study to assess the neuropsychological status of 151 polydrug users, the Halstead-Reitan Neuropsychological Battery showed deficits in 37% 2 to 3 weeks after they entered treatment and in 34% at 3-month followup. Comparative rates for a group of psychiatric patients were 26% and 27%, and for nonpatients, 8% and 4%. Extensive and intensive use of central nervous system depressants and opiates correlated positively with neuropsychological deficit. Older, less educated subjects with adverse medical or developmental histories were more likely to show polydrug related organic impairment. Although there is some evidence that such impairment is reversible, the condition appears to be of at least intermediate duration and may be long-lasting. 6 references. (Journal abstract)

002671 Hankowitz, M.; Lasthaus, P. Westfalisches Landeskrankenhaus, Parkallee 10, D-4540 Lengerich, Germany **/Chronic neuroleptic use and peripheral motor neuron damage./** Chronischer Neuroleptikagebrauch und Schaden im Bereich des peripheren motorischen Neurons. Pharmakopsychiatrie/Neuro-Psychopharmakologie (Stuttgart). 10(1):41-44, 1977.

Electroneurographic and electromyographic studies were performed in 37 patients (average age 39) who had received neurolpetic medication for at least 5 yr. Thirty of the patients had been taking neuroleptics for more than 10 yr. Neuroleptics used were chlorpromazine, thioridazine, levomepromazine, pimozide, clopenthixol, and fluspirilene. Nerve conduction velocity was determined in the right ulnar and fibular nerves and terminal conduction time was measured in the right abductor digiti quinti muscle and right extensor digitorum brevis muscle of the foot. Finally, a needle electromyogram was done under rest, light innervation, and maximal innervation of the abductor digiti quinti and anterior tibialis muscles. Abnormally slow conduction of the ulnar nerve was found in one patient and abnormally slow conduction of the fibular nerve in five patients. One patient showed abnormal terminal conduction of the extensor digitorum brevis muscle of the foot. Six patients showed deviation from the mean in muscle action potentials, but these deviations were less marked than in alcoholics. The deviations found may be caused by slight anticholinergic action of major tranquilizers. 16 references.

002672 Helson, Lawrence; Duque, Luz. Memorial Sloan-Kettering Cancer Center, New York, NY 10021 **Acute brain syndrome after propranolol.** Lancet (London). No.8055:98, 1978.

In a letter to the editor, the case of a 12-year-old girl who presented acute brain syndrome following propanolol treatment for hypertension and lymphoma is discussed. Following anticancer chemotherapy, oral propranolol was administered, 10 mg every 8 hours for three doses, and 15 mg every 8 hours for five doses, in an attempt to control hypertension. Disorientation and agitation were followed by a comatose state without localizing signs. Electroencephalogram revealed a markedly slow and disorganized pattern, and a computerized tomographic scan of the head revealed a small irregular low-density area in the right parietal region which did not change after contrast was injected. Propanolol was stopped after the eighth administration. Symptoms progressed until 80 hours later, when she became rapidly alert and oriented despite no memory of the preceding 3 days. 1 reference.

002673 Horowitz, Frances Degen; Ashton, Jennifer; Culp, Rex; Gaddis, Ed; Levin, Stanley; Reichmann, Brian. Dept. of Human Development and Family Life, University of Kansas, Lawrence, KS 66045 **The effects of obstetrical medication on the behavior of Israeli newborn infants and some comparisons with Uruguayan and American infants.** Child Development. 48(4):1607-1623, 1977.

The effects of obstetrical medication on neonatal behavior were studied using a sample of Israeli infants from medicated and nonmedicated mothers. Of the 65 mothers sampled, 31 had received some type of medication during labor and delivery, including meperidine, Phenergan, and Valium. Few significant behavioral differences were detected in the first month of life, and there was no difference in Bayley Infant Scale performance at 3 months of age. Comparative analyses using samples of American and Uruguayan infants and additional data from other studies of American newborns led to the conclusion that light levels of obstetrical medication do not appear to have significant effects on neonatal behavior. However, this may well be qualified by some initial population differences, by the measurements commonly used in the studies reviewed, and possibly by critical cutoff points dividing the levels of medication that will and will not affect neonatal behavior. 15 references. (Author abstract modified)

002674 Horowitz, Joy. no address **The hidden cost of mind medicines.** Human Behavior. 7(5):52-55, 1978.

The drug induced neuromuscular disorder tardive dyskinesia is discussed to illustrate the dilemma surrounding the long-term side-effects of psychotropic drugs. It is pointed out that tardive dyskinesia can often be reversed in the early stages, but since continued use of phenothiazines can mask its symptoms, it is often not diagnosed in early stages. The rhythmic and involuntary movements that characterize the syndrome are described. Tardive dyskinesia poses a therapeutic dilemma for psychiatrists who must decide in which cases the risks of the syndrome are justified by the probability of cure, and where psychiatric impairment is a worse risk than permanent physical disability. It is concluded that monitoring systems are needed to identify patients with tardive dyskinesia in hospital settings and the community, and long-term followups should be conducted to determine factors that affect the risk of developing tardive dyskinesia.

002675 Ishiguro, T. no address **Waking stage 1-REM observed in paranoid hallucinatory states of narcolepsy.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):499, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, a waking stage-1 REM EEG pattern in paranoid hallucinatory states of narcolepsy is reported. Among four narcoleptic patients who had developed paranoid hallucinatory states, longitudinal investigations were performed of clinical observations and polygraphic manifestations. On clinical observation, periodical exacerbation and remission of narcoleptic syndromes was recognized in all cases, and relapses, especially associated with REM sleep, sometimes developed into paranoid hallucinatory states. Under these states patients could report the contents of their hallucinations in a sleepy voice while they were experiencing them. At this time polygraph recording showed a peculiar pattern which was characterized by stage 1 EEG, REM bursts, and tonic EMG. It was named waking stage 1 REM. Nocturnal polygraphic recordings revealed a very high ratio of waking stage 1 REM and no increment of percentage of stage REM. Immediately preceding and following paranoid hallucinatory states, brief sleep onset stage REM was repeatedly observed in each 30 minute record. These findings suggest that, in paranoid hallucinatory states, there is an impairment of inhibitory mechanisms controlling REM sleep, and that increasing REM sleep pressure caused by persistent use of drugs, for example, tricyclic antidepressants, would eventually let REM sleep intrude into the waking life. Thus these states of narcolepsy were considered to be caused by REM sleep disorders, and waking stage 1 REM was considered as the appearance of the phasic events of REM sleep in stage-W dissociated from its tonic events. (Author abstract modified)

002676 Jones, William N. Univ. of Arizona, Clinical Pharmacy Section/Clinical Pharmacology Section, Tucson, AZ 85724 **Drug-induced systemic lupus erythematosus.** Arizona Medicine. 35(1):16-19, 1978.

In a discussion of drug induced systemic lupus erythematosus, the relationships between several psychopharmacological agents and systemic lupus erythematosus are noted. Reserpine and alpha-methyldopa are known to have induced systemic lupus erythematosus. In a five year study in two mental hospitals, antipsychotic induced systemic lupus erythematosus was diagnosed eight times in a population of 4300 patients. Patients taking chlorpromazine continuously for prolonged periods have antinuclear factors in their blood in about 24% of cases. If symptoms of systemic lupus erythematosus appear, they are usually mild and improve gradually. 20 references.

002677 Jus, A.; Villeneuve, A.; Gautier, J.; Jus, K.; Villeneuve, C.; Pires, P.; Villeneuve, R. Research Division, Dept. of Psychiatry, Centre hospitalier Robert-Giffart, Beauport, P.Q., Canada **Deanol, lithium and placebo in the treatment of tardive dyskinesia.** Neuropsychobiology (Basel). 4(3):140-149, 1978.

The effects of deanol, lithium and placebo on tardive dyskinesia in chronic schizophrenic patients (n=29) were examined using a double-blind crossover design. In addition to the patient's usual treament with different neuroleptics, each patient received either deanol, lithium carbonate or placebo during an 8-week period. A 4-week washout period was inserted between each of the 8-week periods of experimental treatment of tardive dyskinesia. Results indicate that addition of either deanol, lithium carbonate or placebo to the neuroleptic treatment of schizophrenic patients did not produce a statistically significant improvement of tardive dyskinesia. 28 references. (Author abstract modified)

002678 Klimek, Andrzej; Pozniak-Patewicz, Ewa. Klinika Neurologiczna Instytutu Chorob Ukladu Nerwowego i Narzadow Zmyslow AM, ul. Kopcinskiego 22, 90-153 Lodz, Poland /**"Drug dependence" in propranolol treatment of migraine.**/ W sprawie "lekozaleznosci" w czasie leczenia migreny propranololem. Wiadomosci Lekarskie (Warszawa). 30(10):779-781, 1977.

The problem of drug dependence in propranolol treatment of migraine was investigated. Propranolol was originally given to 80 patients with severe headaches, of whom 40 suffered from migraine. All patients experienced a cessation of headache after the 3rd month treatment. At about 1 or 2 weeks after propranolol withdrawal 4 of the patients experienced severe and more frequent recurrence of migraine. These headaches were controlled by a lower dosage, but continuous treatment was required. No explanation has yet been found for drug dependence in propranolol treatment. 9 references.

002679 Kripke, D. F.; Lavie, P.; Hernandez, J. Dept. of Psychiatry (116), V.A. Hospital, 3350 La Jolla Village Dr., San Diego, CA 92161 **Polygraphic evaluation of ethchlorvynol (14 days).** Psychopharmacology (Berlin). 56(2):221-223, 1978.

A full scale polygraphic examination and determination of the effectiveness of ethchlorvynol in improving mood was conducted. Ethchlorvynol (500mg) was administered to four young insomniacs for 14 days as part of a standard 22 day sleep laboratory protocol. Subjects slept more while receiving drug, but these benefits were not statistically significant. Ethchlorvynol impaired mood during both drug and withdrawal periods as compared to baseline, and serious side-effects were reported. Stage REM and stage 1 were suppressed by ethchlorvynol, and stage 1 (but not stage REM) showed withdrawal rebound. Given such data, and the manufacturer's warning against long-term use, no circumstances are considered appropriate for ethchlorvynol prescription. 4 references. (Author abstract modified)

002680 Kudrin, A. N.; Davydova, O. N.; Krendal', F. P. Kafedra farmakologii, Farmatsevticheskiy fakul'tet, I Moskovskiy meditsinskiy institut im. I. M. Sechenova, Moscow, USSR /**Pharmacological incompatibility of neuroleptics and tranquilizers with other preparations.**/ Farmakologicheskaya nesovmestimost' neyroleptikov i trankvilizatorov s drugimi lekarstvennymi sredstvami. Zhurnal Nevropatologii i Psikhiatrii imeni S. S. Korsakova (Moskva). 77(4):587-591, 1977.

A review of literary data and original data concerning the pharmacological incompatibility of psycholeptic drugs and tranquilizers with other preparations is presented. The interaction and effects of methylphenidate with drugs such as trifluoperazine, transamine, reserpine, among others, are discussed. Some practical recommendations for rational use of psychotropic drugs are given. 26 references. (Journal abstract modified)

002681 Lader, Malcolm. Institute of Psychiatry, University of London, London, England **Allergy to diazepam.** British Medical Journal (London). No. 6067:1033, 1977.

Correcting a misquoted statement in a letter to the editor on allergy to diazepam to the effect that desmethyldiazepam is the active and common metabolite of all benzodiazepines, the organic chemistry of benzodiazepines is briefly reviewed. Desmethyldiazepam is the common metabolite of diazepam, medazepam, and clorazepate. Oxazepam is a metabolite of desmethyldiazepam and, like its chlorinated derivative, lorazepam, is metabolized by conjugation with glucuronic acid and then excreted. Nitrazepam and flurazepam have different metabolic chains. It is asserted that cross-allergenicity between the benzodiazepines cannot be automatically attributed to desmethyldiazepam. 1 reference.

002682 Lenz, G.; Konig, P.; Kufferle, B. Psychiatrische Universitatsklinik Wien, Lazarettgasse 14, A-1097 Wien, Austria /**Lithium intoxication masked by neuroleptic drugs when lithium-diuretic combinations are used.**/ Durch Neuroleptika kaschierte Lithium-Intoxikation bei der Kombination Lithium-Saluretikum. Nervenarzt (Berlin). 48(11):630-631, 1977.

The mechanisms of lithium intoxication for lithium/diuretic combinations and the possible involvement of simultaneous treatment with neuroleptic drugs are discussed. The manic-depressive patient described was taking lithium carbonate and haloperidol therapeutically. Upon administration of hydrochlorothiazide for what was considered a mild condition, intoxication symptoms appeared including vomiting, diarrhea, tremors, depression, sleepiness, dizziness, and dysarthric disturbances with unclear speech, which were misinterpreted as a neuroleptic Parkinson syndrome. The patient's condition became critical, and even after a year a psychosyndrome remained. Intoxication resulted from increased lithium reabsorption in the proximal tubules together with a sodium deficiency caused by the diuretic. It is recommended that lithium salt/diuretic combinations only be administered cautiously with weekly monitoring. 6 references. (Author abstract modified)

002683 Levene, M. I. Dept. of Pediatrics, Charing Cross Hospital, Fulham Palace Road, London W6, England **Retention of urine in the neonate possibly due to anticonvulsant drugs.** Archives of Disease in Childhood (London). 52(12):975-977, 1977.

Three cases of acute retention of urine in neonatal patients are reported. The common feature among the cases were birth by caesarean section, severe birth asphyxia, poorly controlled neonatal seizures, and the need for anticonvulsant drugs. Diazepam was administered in each case and is believed to have caused the urine retention. It is concluded that diazepam may have inhibited micturition by depressing the nervous system. 2 references.

002684 Levy, Micha; Kletter-Hemo, Dina; Nir, Isaac; Eliakim, Marcel. Clinical Pharmacology Unit, Hadassah University Hospital, Jerusalem, Israel **Drug utilization and adverse drug reactions in medical patients: comparison of two periods, 1969-72 and 1973-76.** Israel Journal of Medical Sciences (Jerusalem). 13(11):1065-1072, 1977.

A study of drug usage patterns and adverse drug reactions in Jerusalem was carried out on 2771 hospitalized medical patients during 1969 to 1976. Comparison of data between 1969 and 1972 and 1973 to 1976 shows an 11% reduction in the average number of drugs per patient, and a 59% decrease in the incidence of adverse effects, calculated as percent of all exposures. Among the drugs monitored were diazepam and nitrazepam; adverse reactions to these were minimal. The number of patients affected by adverse reactions during the second period fell by 61%. These data seem to indicate that there was considerable improvement in habits of drug usage in the monitored ward. 23 references. (Author abstract modified)

002685 Lutz, Elmar G. 896 Valley Road, Wayne, NJ **Acute lithium-induced parkinsonism precipitated by liquid protein diet.** Journal of the Medical Society of New Jersey. 75(2):165-166, 1978.

A case report of a 55 year old female with manic depressive illness since adolescence, is reported, in which self-administered liquid protein diet was responsible for the toxic rise of serum lithium with sudden extrapyramidal system decompensation in the form of parkinsonism. Discontinuation of the diet resulted in dramatic symptom reversal. Possible pathogenetic factors are discussed. Careful monitoring of medicated patients on long-term diet therapy is considered mandatory. 6 references. (Author abstract modified)

002686 MacGregor, Gerald A. St. Luke's Hospital, Guildford, Surrey GU1 3NT, England **Hyperthyroidism and a parathyroid adenoma complicating lithium treatment.** Lancet (London). No.8048:1129-1130, 1977.

In a letter to the editor a relationship between hyperthyroidism, parathyroid adenoma, and lithium treatment for depression is reported, with an illustrative case history. The thyroid and parathyroid glands are embryologically closely related and both can be affected by lithium. The drug interferes with thyroid secretion and more iodine collects in the gland. Hyperparathyroidism is at first asymptomatic, and 20% of cases have also shown thyroid abnormalities. Hypersecretion and sometimes later gland failure, occurs in sarcoidosis, when the granulomas infiltrate the thyroid or parathyroid gland. It is suggested that the infrequent endocrinopathies seen in lithium treated cases apparently arise from earlier and similar immune processes.

002687 Maruta, Toshihiko. Mayo Clinic, Rochester, MN 55901 **Prescription drug-induced organic brain syndrome.** American Journal of Psychiatry. 135(3):376-377, 1978.

Two cases of prescription drug induced organic brain syndrome are presented, and the importance of early intervention in prescription drug abuse is emphasized. In case one, the patient who received propoxyphene napsylate, aspirin, diazepam and flurazepam for back pain did not note his gradual intellectual deterioration, until he was returned to his normal status. In the second case the patient was abusing glutethimide and diazepam, was obtaining good symptomatic relief from the medications, and continued to receive prescriptions, however, this was at the price of progressive deterioration of personality and cognitive functioning. It is recommended that physicians review regularly and in detail the medications used by their patients to prevent subtle but serious changes in personality, cognitive functioning, or both. 5 references.

002688 Mehta, Dinesh; Mallya, Ashok; Volavka, Jan. Missouri Institute of Psychiatry, 5400 Arsenal Street, St. Louis, MO 63139 **Mortality of patients with tardive dyskinesia.** American Journal of Psychiatry. 135(3):371-372, 1978.

Studies were conducted to determine whether tardive dyskinesia may reduce life expectancy. Thirty-five geriatric patients from a state mental hospital with varying degrees of tardive dyskinesia were matched with 35 unaffected controls. At 5 year followup 19 experimentals and 12 controls were dead. Severity ratings of the patients who had died were four mild, five moderate, eight severe; the respective numbers for surviving patients were three, nine and two. It is concluded that the findings do not necessarily indicate a causal relationship as it is not known what mechanisms are involved. 5 references.

002689 Mellerio, F. no address **Electroencephalographic peculiarities during acute drug intoxications in epileptic patients.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):495, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, EEG peculiarities during acute drug intoxications in epileptic patients are described. In cases of acute long-acting barbiturate intoxications (phenobarbital), the same electroencephalographic perturbations are seen in nonepileptic and epileptic patients. However, certain characteristics may raise the suspicion of epilepsy. Spike and complexes and polyspikes suggest epilepsy, but these paroxysmal abnormalities are rarely observed during barbiturate coma, they reappear only several days after intoxication (when the serum phenobarbital level is low). Asymmetry indicates a neurological process associated with the poisoning, and possibly epilepsy. Another very suspect pattern is slow-waves and slow spikes mixed with rapid rhythms. The same picture is often observed with short-acting barbiturate intoxications in a nonepileptic population but is unusual with phenobarbital in nonepileptic patients and frequently encountered among epileptic subjects. This highly suspect pattern is an indication to repeat the registrations several days after poisoning to detect paroxysmal features. Nonbarbiturate anticonvulsant intoxications can be associated with phenobarbital, without supplementary modifications. Antidepressive tricyclic poisonings are exceptionally observed in an epileptic population; it is possible that their activating (phenothiazine) or convulsant action (tricyclic drugs) are potentiated in these cases. Disturbance of cerebral electrogenesis are very important during acute drug intoxications and the diagnosis of epilepsy rarely assured in this period, but some suspicious patterns require repeated registrations to detect epilepsy. (Author abstract modified)

002690 Okada, Fumihiko; Kase, Manabu; Shintomi, Yoshiko; Asano, Yutaka; Naganuma, Toshiyuki; So, Taiji. University of Hokkaido Health Admininstration Center, Hokkaido, Japan **Autonomous nervous function of long-term users of psychotropic drugs, third report -- pupilogram observations.** Psychiatria et Neurologia Japonica (Tokyo). 79(5):259-260, 1977.

At the 50th Hokkaido Symposium for Neuropsychiatrists held in December 1976 at the Hokkadio Medical School, Japan, the results of examination of 16 mental patients who had been taking psychotropic drugs for a long period of time were presented. Reactions to an infrared pupilograph (contraction of pupils) were measured. The patients were divided into three groups by the extent of their mental disorder. In group 1 (7 persons) readings averaged 357.7plus or minus 11.3msec. Group 2 (5 persons) was 304.0plus or minus 9.8msec. Group 3 (4 persons) was 275.0plus or minus 5.0msec. The control group of normal persons was 254.0plus or minus 10.8msec. There was a significant difference in the times between groups 1 and 2. The meaning of differences between other groups was also discussed.

002691 Overall, John E. University of Texas Medical Branch, Galveston, TX **Prior psychiatric treatment and the development of breast cancer.** Psychopharmacology Bulletin. 14(1):19-20, 1978.

A paper read at the annual meeting of the New Clinical Drug Evaluation Units of NIMH in Key Biscayne, FL, May 1977, on the relationship between prior psychiatric treatment and the development of breast cancer is presented. A retrospective epidemiological study of women 40 years of age or younger who sought treatment at a regional hospital for either psychiatric disturbances or breast cancer was undertaken. It is concluded that the probability of prior psychiatric treatment is essentially identical in the breast cancer and other cancer groups and that the hypothesized rela-

tionship between treatment with prolactin stimulating antipsychotic drugs and development of breast cancer in humans is not great enough to be a major consideration in the clinical use of psychotherapeutic drugs.

002692 Parkes, J. D. Department of Neurology, King's College Hospital, Denmark Hill, London SE5 94S, England **The sleepy patient.** Lancet (London). No. 8019:990-993, 1977.

Excessive daytime sleep in 184 patients seen over a 5 yr period is discussed. The most common diagnosis was narcoleptic syndrome. Nearly all narcoleptic patients show disordered night sleep with extreme restlessness and frequent awakening, and about one fourth have frequent periods of automatic behavior during the daytime when they are only half awake and often behave inappropriately. The occurrence of cataplexy, sleep paralysis, or both is necessary for diagnosis of the narcoleptic syndrome. Patients have been treated with amphetamine, methylphenidate, and clomipramine. Narcolepsy can occur alone. Seven patients were seen with the Kleine-Levin syndrome, in which an initial period of overeating is followed by a subsequent period of prolonged sleep. Other conditions discussed are sleep reversal, somnambulism, and sleep apnea. On the whole, cerebrovascular disease does not cause narcolepsy. 15 references.

002693 Preskorn, Sheldon H.; Biggs, John T. Washington University School of Medicine, St. Louis, MO 63110 **Use of tricyclic antidepressant blood levels.** New England Journal of Medicine. 298(3):166, 1978.

In a letter to the editor, the use of tricyclic antidepressants is discussed with reference to the case of a 50-year-old woman with a history of depressive disorder. Amitriptyline, at a dose of 150mg by mouth daily, relieved her depressive symptoms, but anxiety, dryness of mouth, constipation and tremors were reported after 1 month of treatment. The patient also presented acute organic brain syndrome, recent memory impairment, confusion, ataxia, and paranoid delusions prior to discontinuation of the medication. Reduction of dose to 50mg amitriptyline daily proved effective in clearing all side-effects. The case emphasizes the need for routine availability of prompt, accurate tricyclic measurements to avoid the risks of overdosage. 5 references.

002694 Rosenow, Edward C., III. Mayo Medical School, Rochester, MN **Drugs that may induce pulmonary disease.** Geriatrics. 33(1):64-68, 73, 1978.

In a discussion of side-effects of therapy in geriatric patients, drugs that may induce pulmonary disease (including several psychotropic medications) are listed. Methadone, propranolol, and chlordiazepoxide are psychotropic agents which may be dangerous for elderly patients. Although these patients may not be more susceptible than others to drug induced pulmonary disease, they are usually taking numerous drugs, which may interact and sensitize the lungs to a potential adverse reaction. The corticosteroids also have been indicated for pulmonary disease -- usually opportunistic infections or mediastinal klipomatosis. A report which described three patients who had pleural effusion and two other who had diffuse pulmonary disease while taking beta-adrenergic blockers is noted. 13 references.

002695 Rossof, Arthur H.; Fehir, Kim M. Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL 60612 **Lithium stimulation of granulopoiesis.** New England Journal of Medicine. 298(5):280-281, 1978.

In a letter to the editor, it is contended that sufficient data exist to conclude that lithium increases granulocyte production in vivo. It has been found that the unsaturated vitamin B12 binding capacity, an indirect assessment of the total body granulocyte pool, is elevated in patients taking lithium for manic-depressive psychosis; that lithium stimulated production of colony stimulating activity (CSA) by mouse lung in vitro; and that the levels of urine and serum CSA from patients with Felty's syndrome given lithium are increased from their low basal values. A canine model of lithium induced granulocytosis is described. 5 references.

002696 Saraf, Kishore R.; Klein, Donald F.; Gittelman-Klein, Rachel; Gootman, Norman; Greenhill, Philip. Dept. of Psychiatry, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY 11040 **EKG effects of imipramine treatment in children.** Journal of the American Academy of Child Psychiatry. 17(1):60-69, 1978.

The effects of imipramine treatment are studied in both hyperactive and phobic children, with attention to the electrocardiograms (EKGs) obtained in children during imipramine therapy. Analysis of the EKG effects of imipramine in 25 hyperactive and eight school phobic children suggests that children on a dose of imipramine of 3.5mg/kg or more are likely to show an increase in PR interval of .02 seconds or more, and that such increases are more likely to occur in patients with a small pretreatment PR interval. In seven children the PR interval prolongation was above the rate corrected norm. EKG monitoring seems desirable in children maintained on imipramine dose of 3.5mg/kg or more. 28 references. (Author abstract modified)

002697 Schyve, Paul M.; Smithline, Francine; Meltzer, Herbert Y. Illinois State Psychiatric Institute, Chicago, IL **Prolactin and breast cancer.** Psychopharmacology Bulletin. 14(1):17-19, 1978.

A paper read at the annual meeting of the New Clinical Drug Evaluation Units of NIMH in Key Biscayne, FL, May 1977, which reviews research on the relationship between prolactin elevating neuroleptics and breast cancer in humans is presented. No association has been established between increased plasma prolactin levels and breast cancer in humans. However, a fraction, perhaps up to 30% of human breast tumors may be prolactin dependent. In patients susceptible to or bearing such tumors, the use of prolactin stimulating antipsychotics may be relatively contraindicated. Since such persons cannot yet be identified, no changes in current prescribing habits are suggested. 32 references.

002698 Siegel, Ronald K. Psychopharmacology Unit, Research Trailer 350, Brentwood V.A. Hospital, Los Angeles, CA 90073 **Cocaine hallucinations.** American Journal of Psychiatry. 135(3):309-314, 1978.

The literature on hallucinations that occur as a result of acute and chronic cocaine administration is reviewed, and the phenomenology of cocaine hallucinations in a group of 85 recreational cocaine users, 15 of whom reported hallucinatory experiences in visual, tactile, olfactory, auditory, and gustatory modalities is examined. A new phenomenon of snow lights is discussed in terms of initiating a progression of symptoms leading to the classic cocaine bugs. The similarity of cocaine hallucinations to entoptic phenomena and migraine hallucinations, which suggests a common mechanism of action based on CNS excitation and arousal is elucidated. 46 references. (Author abstract modified)

002699 Simpson, George M.; Lee, J. Hillary; Shrivastava, Ram K. USC Metro Unit, Metropolitan State Hospital, 11400 South Norwalk Boulevard, Norwalk, CA 90650 **Clozapine in tardive dyskinesia.** Psychopharmacology (Berlin). 56(1):75-80, 1978.

To evaluate the clinical efficacy and possible side-effects of clozapine in the treatment of tardive dyskinesia, 12 male and female chronic schizophrenic inpatients with tardive dyskinesia were administered clozapine for an 18 week period. Its antipsychotic activity was again demonstrated and it suppressed the symptoms of tardive dyskinesia with a marked rebound occurring in these symptoms when it was withdrawn; there was no rigidity or other parkinsonian symptoms. However, out of a total of 12 patients, neutropenia (800 and 1120) occurred in two patients, convulsions in one patient, marked withdrawal effects in three patients, and a hypotensive collapse with atrial fibrillation in one patient. If these adverse effects are confirmed in a larger sample size, then despite the novel desirable effects of clozapine it would seem unlikely that it will gain widespread or routine use. 7 references. (Author abstract modified)

002700 Singh, R. B.; Singh, V. P.; Somani, P. N. Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India **Psychosis: a rare manifestation of digoxin intoxication.** Journal of the Indian Medical Association (Calcutta). 69(3):62-63, 1977.

A case of psychosis with atrial fibrillation and ventricular premature beats due to digoxin toxicity is presented. Serum digoxin level was 2.9ng/ml and serum magnesium 1.2mEq/1. Digoxin should be considered as one of the causes in the differential diagnosis of psychosis especially in cardiac patients receiving dogoxin. 9 references. (Author abstract)

002701 Sobczyk, Wanda; Dowzenko, Anatol; Krasicka, Jadwiga. Instytut Psychoneurologiczny, Sobieskiego 1/9, 02-957 Warsaw, Poland **/Investigations of children of mothers treated in pregnancy with anticonvulsants./** Badania dzieci matek leczonych w czasie ciazy lekami przeciwpadaczkowymi. Neurologia i Neurochirurgia Polska (Warszawa). 11(1):59-65, 1977.

A study of the effects of anticonvulsants administered to epileptic women during pregnancy is presented. Twenty-seven medical histories were analyzed relative to course of maternal epilepsy, and treatment during pregnancy and during labor. Forty case histories of the children of these mothers were examined for neonatal condition, and psychological and EEG findings. Results showed an incidence of pregnancy disorders (20.5%) higher than the general population. Numerous minor malformation syndromes were found in these children (37.5%), somatic development was deficient in 52.5% of cases, and EEG abnormalities were present in 65.6%. No abnormalities were observed in mental development. Results indicate that abnormalities were most frequent when the mothers had been treated with derivatives of phenytoin and phenobarbital. 15 references. (Journal abstract modified)

002702 Solomon, Kenneth. Dept. of Psychiatry, Medical College of Virginia, Richmond, VA 23298 **Safety of oxazepam.** New York State Journal of Medicine. 78(1):91-92, 1978.

A case of large nonfatal overdose of oxazepam, 2400mg, is reported. The literature is reviewed and reveals only four other cases of overdose with oxazepam. The drug is found to have a wide margin of safety. In the case reported, the patient remained in a state of light sleep for approximately 24 hours, during which time the only physical abnormality noted was pupillary constriction. He was arousable at all times and recovered fully without any medical treated and no observable sequelae. It is mentioned that other benzodiazepines seem similarly safe when taken as an overdose or as a large therapeutic dose. 11 references.

002703 Stevens, Janice R. University of Oregon Health Sciences Center, Portland, OR 97201 **Eye Blink and schizophrenia: psychosis or tardive dyskinesia?** American Journal of Psychiatry. 135(2):223-226, 1978.

In an investigation of 44 medication free schizophrenic patients, increased spontaneous blinking and decreased reflex blinking in relation to dopamine hypotheses of the pathophysiology of schizophrenia were examined. Extraocular muscle activity and EEG were recorded by radiotelemetry during free behavior and sleep for 2 to 24 hours. Abnormalities of ocular movement including abnormal blink rate and blink reflex to glabellar tap were found in 34 of 44 patients. It could not be established whether these signs represent part of the pathology of schizophrenia or result from withdrawal of neuroleptic treatment. 19 references.

002704 Taylor, Rodney H.; Menzies-Gow, N.; Lovell, D.; La Brooy, S. J.; Misiewicz, J. J. Dept. of Gastroenterology/Histopathology, Central Middlesex Hospital, London, England **Misleading response of malignant gastric ulcers to cimetidine.** Lancet (London). No.8066:686-687, 1978.

The misleading response of malignant gastric ulcers to cimetidine in four patients is discussed. The ulcers healed and their symptoms disappeared. However, when cimetidine was stopped the symptoms recurred. Intramucosal cancer was found only at histopathological examination of the resected stomachs in two of the four patients, and in all the cases malignance had not been detected by the initial serial biopsies and brush cytology. It was concluded that relief of symptoms of malignant gastric ulcers by cimetidine may delay diagnosis and appropriate treatment. 4 references. (Author abstract modified)

002705 Teutsch, Carol; Brennan, Robert W. Division of Neurology, Department of Medicine, Milton S. Hershey Medical Center, Hershey, PA 17033 **Amanita mushroom poisoning with recovery from coma: a case report.** Annals of Neurology. 3(2):177-179, 1978.

Neurological effects of amanita mushroom poisoning in a 57-year-old woman are reported. Onset of symptoms was delayed. Patient presented as a comatose and mildly hyperneic individual, responding only to noxious stimuli. Clinical and electroencephalographic observations were consistent with severe hepatic encephalopathy and correlated closely with liver function abnormalities. Despite the development of coma, full recovery followed the use of thioctic acid, an experimental therapeutic agent. 8 references. (Author abstract modified)

002706 Tice, Linwood F. Philadelphia College of Pharmacy and Science, 43rd St. and Kingsessing Ave., Philadelphia, PA 19104 **Estrogens: their functions, uses and hazards: part 2.** American Pharmacy. NS18(2):30-33, 1978.

Uses and hazards of estrogens are reviewed with special reference to their prevalence in menopausal therapy for women. Estrogens are used to diminish menopausal symptoms such as hot flashes, vaginal irritation, and menstrual regulation. Their use in controlling emotional conditions related to menopause is contraindicated, and short-term or cyclical therapy is recommended rather than chronic medication. Es-

trogens have been labeled as potential carcinogens and as causing cardiovascular problems. Prescription of estrogens is advised on the basis of whether anticipated benefits outweigh known risks, which must be communicated to the patient in order to reach an acceptable decision for therapy.

002707 Timberlake, William H.; Vance, Michael A. Lemuel Shattuck Hospital, 170 Morton Street, Jamaica Plain, MA 02130 **Four-year treatment of patients with parkinsonism using amantadine alone or with levodopa.** Annals of Neurology. 3(2):119-128, 1978.

Both acute and long-term effects of amantadine alone or in combination with levodopa were undertaken in 94 parkinsonism patients to examine side-effects and efficacy. Half of the patients improved on amantadine therapy during acute double-blind trials. In a 4 year followup, amantadine given alone or added to a stable dose of levodopa had its greatest effect in the first month and helped few patients after 6 months. Levodopa either alone or added to a stable dose of amantadine had a beneficial effect lasting 3 years or more. The side-effects of edema and livido reticularis occurred twice as often in women. Confusion and hallucinations appeared sooner on a regimen of 300mg of amantadine a day, but the ultimate incidence was the same on 200mg a day. Withdrawal effects from amantadine are no less frequent or serious than from other antiparkinson medications and are not evidence that amantadine is still helping the patient. Considering the years of exposure, the morbidity and mortality do not indicate any risks peculiar to amantadine. Mortality in all groups combined was 2.4times that of the age and sex matched United States population. While the beneficial effects of amantadine are definite, they are brief. Central side-effects and problems of withdrawal suggest careful consideration in decision to use amantadine. 23 references. (Author abstract modified)

002708 Topliss, Duncan; Bond, Rodney. Ewen Downie Metabolic Unit, Alfred Hospital, Prahran, Victoria, Australia **Acute brain syndrome after propranolol treatment.** Lancet (London). No.8048:1133-1134, 1977.

In a letter to the editor, a case history of a patient who developed acute brain syndrome after propranolol treatment is presented. Although the most common mental side-effect of propranolol is central nervous dysfunction with visual hallucinations and depression, the patient discussed presented an organic brain syndrome when administered propranolol for a tremor associated with a tax multimodular goiter. The mental deterioration was resolved rapidly when the drug was stopped. It is suggested that potential confusion between thyroid storm and a drug induced side-effect should be considered when there is a mental deterioration during treatment for hyperthyroidism.

002709 Van Putten, Theodore. VA Hospital, Wilshire & Sawtelle Boulevards, Los Angeles, CA 90073 **Drug refusal in schizophrenia: causes and prescribing hints.** Hospital & Community Psychiatry. 29(2):110-112, 1978.

Causes of drug refusal in schizophrenic patients are reviewed and prescribing hints to remedy the situation are presented. Research is cited which indicates that many discharged patients diagnosed as schizophrenic do not continue to take their prescribed antipsychotic medication. Reasons for reluctance to take drugs include the development of extrapyramidal symptoms, most notably akathisia and akinesia; a poor doctor-patient relationship; or the patient's preference to continue his schizophrenic existence. To improve drug compliance, it is suggested the physician should ask the patient about his impressions of side-effects and should let the patient help determine the optimal dosage. 11 references. (Author abstract modified)

002710 Volk, W. Forschungsstelle fur Psychotherapie, Christian-Belser-Strasse 79 A., D-7000 Stuttgart 70, Germany **/Hypotonic circulatory disorders under psychopharmacotherapy -- treatment with 9-alpha-fluorohydrocortisone./** Hypotone Kreislaufregulationsstorungen unter Psychopharmakamedikation. Zur Behandlung mit 9-alpha-Fluorhydrocortison. Medizinische Welt (Stuttgart). 28(45)1853-1854, 1977.

A study of the use of the mineralocorticoid 9-alpha-fluorhydrocortisone in the treatment of psychopharmacotherapeutically induced orthostatic hypotension is reported. Thirteen patients (seven females and six males), including 12 schizophrenics and one endogenous depressive, were divided into three groups, administered 9-alpha-fluorohydrocortisone, the sympathomimetic norfenefrine, and placebo, respectively, in a double-blind trial. The Schellong test administered before the trial, and at three weekly intervals, showed definite differences between the three groups. The 9-alpha-fluorohydrocortisone group showed a drop from 3 to 2 in average Schellong pathological test value. It is interesting to note that placebo patients showed better final test values than those receiving norfenefrine. 21 references.

002711 Wheatley, David. no address **Stress and the heart: interactions of the cardiovascular system, behavioral state, and psychotropic drugs.** New York, Raven, 1977. 262 p. $15.00.

Clinical and experimental studies dealing with circulatory disorders and psychiatric illness are presented. Four main topics -- coronary disease and anxiety, psychotropic drugs and the heart, stress factors in hypertension, and psychopharmacological aspects of cerebral circulation -- are covered. Widely disparate areas such as emotional stress in the etiology of coronary heart disease and ECG changes with psychotropic drugs are included. Contributions from a number of authors including pharmacologists, psychiatrists, pathologists and a cardiologist are incorporated.

002712 Zoffuto, Anthony; Trapp, Charles A. Dept. of Medicine, VA Hospital, 1030 Jefferson Ave., Memphis, TN 38104 **Lithium-induced hypothyroidism.** Southern Medical Journal. 70(12):1455-1458, 1977.

The case of a 58-year-old man presenting somnolence, cold intolerance, and dry scaly skin, and diagnosed as suffering from thyroprival hypothyroidism secondary to lithium is discussed with reference to the general pharmacology of lithium. For several years, the patient had taken lithium for effective control of a circular manic-depressive state. In such cases lithium therapy is of such value that it is desirable to continue treatment with lithium despite undesirable side-effects. Pharmacological treatment of these side-effects can then be used to supplement the lithium therapy. In the patient under discussion, the hypothyroidism was controlled by thyroid replacement therapy and he continued to receive lithium for control of manic-depressive symptoms. 4 references.

16 METHODS DEVELOPMENT

002713 Chiarenza, G. A.; Giordana, F.; Maffei, C.; Penati, G.; Ponzano, M.; Resele, L.; Rognoni, G. no address **The use of the CNV (contingent negative variation) in the determination of residual effects of five hypnotic drugs.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):562, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, the use of the contingent negative variation (CNV) in the determination of residual effects of five hypnotic drugs is described. An investigation was undertaken to find out whether the CNV could be used as an electrophysiological index to evaluate some long lasting effects of drugs and to compare these data with the results of psychological tests. Eight healthy volunteers were treated with five hypnotic drugs: desmethyldiazepam, diazepam, chlordesmethyldiazepam, amobarbital, and placebo. The drugs were administered in a Latin square design, for two consecutive nights. Testing began 10 minutes after awakening. The tests employed included: simple reaction time, choice reaction time, WAIS digit symbol, and CNV. The results show that the five drugs modify differently the patterns of the CNV. This neurophysiological index seems to be more reliable than psychological tests. (Author abstract modified)

002714 Cooper, Thomas B.; Simpson, George M. Clinical Psychopharmacology Laboratory, Rockland Research Institute, Orangeburg, NY 10962 **Prediction of individual dosage of nortriptyline.** American Journal of Psychiatry. 135(3):333-335, 1978.

A technique that enables a physician to determine individual patient dosage requirements for nortriptyline from a single 24 hour blood sample is described. Because the technique reveals immediately those patients at the extremes of dosage ranges, toxicity and the need for time consuming titration of the dosage regimen can be avoided. The technique as practiced using 18 physically healthy normal volunteers, aged 21 to 51 years, is described. When used successfully, precise tailoring of the medication to each individual patient's needs is made possible, thus minimizing overmedication that could result in untoward side-effects. 12 references. (Author abstract modified)

002715 Creese, Ian; Snyder, Solomon H. Dept. of Pharmacology, Johns Hopkins University School of Medicine, Baltimore, MD 21205 **A simple and sensitive radioreceptor assay for antischizophrenic drugs in blood.** Nature. 270(5633):180-182, 1977.

A radioreceptor assay for neuroleptics based on competition for dopamine receptor binding is described. The technique is simple, sensitive, specific and suitable for routine clinical application. Since the milligram potencies of neuroleptics are closely correlated with their affinity for dopamine receptors labeled with H-haloperidol, the sensitivity of the assay is greater for drugs which are used at low therapeutic doses. The assay can be used in patients who are receiving a variety of other drugs besides neuroleptics, but for patients receiving two or more neuroleptics, the absolute concentration of each drug cannot be separately determined. As many as 100 assays can be conducted in a single morning. 29 references.

002716 Fischman, Marian W.; Schuster, Charles R.; Uhlenhuth, E. H. Dept. of Psychiatry, University of Chicago School of Medicine, 950 East 59th Street, Chicago, IL 60637 **Extension of animal models to clinical evaluation of antianxiety agents.** In: Hanin, I., Animal models in psychiatry and neurology. Elmsford, N.Y., Pergamon Press, 1977. 499 p. (p. 339-349).

In a paper presented at a workshop on animal models in psychiatry and neurology held in Rockville, Maryland, in June 1977, the use of the conditoned avoidance paradigm as an animal model for assessing the clinical effects of phenothiazines is discussed in terms of the problems of using an animal model as a predictor of drug effects on human behavior. Studies in animals of the effects of chlorpromazine and pentobarbital on electric shock avoidance and escape responding are reported, and a procedure using loss of points devised as an alternative to using electroshock as an aversive stimulus in humans is discussed with reference to the effects of several doses of dextroamphetamine, chlorpromazine, imipramine, pentobarbital, and diazepam on responding to avoid loss of points were examined. The point loss avoidance paradigm showed the differential effects of the drugs; i.e.,the selective suppressant effects of phenothiazine drugs found in nonhuman studies, the rate increasing effects of amphetamines, and the more generalized suppressant effects of pentobarbital and diazepam. It is suggested that the studies in humans: 1) confirm the usefulness of the conditioned avoidance paradigm for differentiating the effects of drugs; 2) demonstrate a continuity of behavior from nonhuman models to humans; and 3) rule out the possibility of major species differences in avoidance/escape behavior and in the interaction of that behavior with psychotropic drugs. 34 references.

002717 Howarth, A. T. Bradford Royal Infirmary, Bradford, England **A simple method for the determination of therapeutic levels of clomipramine, imipramine and desipramine.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):131-135, 1977.

A simple method for the determination of therapeutic levels of clomipramine, imipramine, and desipramine is offered. The use of one solvent only is involved and the result is available within three hours, most of this time being required for the development of the chromatograph. The accuracy of measurement and degree of recovery are considered good, as is identification, especially if all three solvents and a subsequent staining technique are used. The process of extraction, purification, and identification which is described could, it is suggested, be employed by many laboratories for assaying plasma concentrations of the tricyclic antidepressants at the request of clinicians. 2 references.

002718 Kellner, R.; Bruzzese, D.; Winslow, W. W.; Rada, R. T.; Wall, F. J. Dept. of Psychiatry, Univ. of New Mexico, Albuquerque, NM **The effects of one-day treatment of anxiety with high doses of halazepam.** Journal of Clinical Pharmacology. 18(4):203-209, 1978.

To examine a one day treatment methodology for the assessment of drug effects and to examine the efficacy of halazepam in the relief of anxiety, a double-blind crossover study of halazepam and placebo was carried out with 22 patients, 20 completing the study. Each treatment lasted for one day. Oral medication was administered starting with a dose of 40mg and the dose adjusted every 2 hours. The total daily dose did not exceed 600mg. Several rating and self-rating scales were used. All observer rating scales and several self-rating scales discriminated for drug effects at a significant level. The design appears to be suitable for the rapid screening for antianxiety properties of new drugs. 13 references. (Author abstract modified)

002719 Lloyd-Evans, S.; Brocklehurst, J. C.; Palmer, M. K. Dept. of Geriatric Medicine, University Hospital of South Manchester, West Didsbury, Manchester M20 8LR, England **Assessment of drug therapy in chronic brain failure.** Gerontology (Basel). 24(4):304-311, 1978.

To differentiate between vascular and ideopathic chronic brain failure in aging people and to aid in the testing of and therapy with pharmaceutical agents, an arteriosclerosis score

was formulated and used to study effects of Piracetam on two groups of nonhospitalized Ss, those with slight intellectual impairment, and those with moderate brain failure. The score was found to correlate closely with the ADL score, but not with the MSQ score, nor with a battery of seven psychological tests. Difficulties in administering medication on a long-term basis to elderly people is also discussed. 16 references.

002720 Moyes, R. B.; Moyes, I. C. A. Dept. of Chemistry, Univ. of Hull, Hull, England **Measurement of plasma antidepressant levels by high-performance liquid chromatography.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):117-123. 1977.

The relationships between dosage of tricyclic antidepressants, the plasma levels they produce, and their clinical effect, were investigated by means of a high performance liquid chromatography (HPLC) technique for the quantitative estimation of clomipramine, amitriptyline, nortriptyline, and desmonomethylclomipramine whereby the eluted sample could be recovered for further analysis by gas liquid chromatography (GLC). Tertiary amines (trimipramine, amitriptyline) were eluted first, then secondary amines (imipramine, nortriptyline), a fact which may be of use in identifying metabolites. It is suggested that combined HPLC and GLC offer a method of identifying drugs in cases of poisoning. 8 references. (Author abstract modified)

002721 Nakano, Shigeyuki; Gillespie, Hamp K.; Hollister, Leo E. Div. of Clinical Pharmacology, Stanford University School of Medicine, Stanford, CA 94305 **A model for evaluation of antianxiety drugs with the use of experimentally-induced stress: comparison of nabilone and diazepam.** Clinical Pharmacology and Therapeutics. 23(1):54-62, 1978.

To study the feasibility of a model for evaluation of antianxiety drugs with the use of experimentally-induced emotional stress, volunteer subjects were used to compare a potential antianxiety drug (nabilone, 2mg single doses) with a standard drug (diazepam, 5mg single doses). A double masked design with placebo control was used. Volunteer subjects were selected on the basis of high levels of trait anxiety and were tested by two anxiety inducing procedures -- the mirror drawing test and the Stroop color/word test. Anxiety induced by the experimental procedure was alleviated by diazepam and, to a lesser extent, by nabilone. Since doses of the two drugs may not have been equivalent, or the time courses identical, conclusions about their relative efficacy are guarded. The experimental model is considered unusual in that antianxiety drugs can be tested in volunteer subjects for true antianxiety effects rather than for side-effects, such as cognitive or motor impairment, sleepiness, or other signs of central nervous system depression. 38 references. (Author abstract modified)

002722 Proctor, Jack, D.; Chremos, Athanassios N.; Evans, Eleanor F.; Wasserman, Albert J. Div. of Clinical Pharmacology, Box 284, Medical College of Virginia, Richmond, VA 23298 **An apomorphine-induced vomiting model for antiemetic studies in man.** Journal of Clinical Pharmacology. 18(2-3):95-99, 1978.

To test the efficacy of an apomorphine-induced vomiting model for antiemetic studies in man, which is more efficient than the usual intravenous titration technique, a uniform dose of 0.05mg/kg apomorphine given subcutaneously to test the antiemetic action of metoclopramide and votracon in ten healthy, young male volunteers. All ten subjects vomited in response to this dose of apomorphine when pretreated with placebo. Pretreatment with metoclopramide prevented vomiting in all subjects, and votracon prevented vomiting in two. Apomorphine, 0.05mg/kg, subcutaneously appears to be an appropriate challenge dose for testing compounds for antimetic activity in normal human volunteers. 14 references. (Author abstract modified)

002723 Read, G. F.; Riad-Fahmy, D.; Walker, R. F. Tenovus Institute for Cancer Research, Heath, Cardiff, Wales **A specific radio-immunoassay procedure for plasma clomipramine.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):110-116, 1977.

A procedure which allows plasma clomipramine concentrations to be assayed without prior separation of possible cross-reactants such as metabolites or other drugs often given concurrently is discussed. Antisera to clomipramine was obtained and used in conjunction with a tritiated clomipramine radioligand to set up a radioimmunoassay. The specifity is described as excellent and precision described as good. The sensitivity was found to be adequate for any studies currently envisaged. The correlation of results obtained in human plasma with those obtained following preassay purification was found to be excellent, confirming the accuracy of the assay in human plasma. 12 references.

002724 Ross, Maureen; Ghazarossian, Vartan; Cox, B. M.; Goldstein, Avram. Addiction Research Foundation, Stanford University, Palo Alto, CA 94304 **Radioimmunoassays for beta-endorphin: comparison of properties of two antisera.** Life Sciences (Oxford). 22(13-15):1123-1130, 1978.

Two antisera are described with antigenic determinants not hitherto reported: one of these is suitable for assays of beta-endorphin in human plasma, the other contains an antibody that recognizes beta-endorphin only if amino terminal Tyr is present, thus achieving a coincidence of immunoreactivity and opioid activity. Development testing, radioimmunoassay procedures, and cross-reactivity studies with the two antisera are outlined. 21 references. (Author abstract modified)

002725 Rubin, Robert T.; Hays, Sally E. Dept. of Psychiatry, UCLA School of Medicine, Harbor General Hospital Campus, Torrance, CA **Profiles of prolactin response to antipsychotic drugs: some methodologic considerations.** Psychopharmacology Bulletin. 14(1):9-11, 1978.

A paper read at the annual meeting of the New Clinical Drug Evaluation Units of NIMH in Key Biscayne, FL, May 1977, on methodological considerations in profiles of prolactin response to antipsychotic drugs is presented. The possibility of a biphasic prolactin response means that monitoring prolactin secretion just until it begins to decline, under the assumption that it will continue in a smooth decline back to baseline, is insufficient. Great interindividual variation in the prolactin response necessitates a sample of sufficient size to permit stable cross Ss averaging, and dictates that the most direct routes of administration available for the drug being tested be employed. 10 references.

002726 Saletu, B.; Grunberger, J. no address **Pharmacodynamic investigations in psychopharmacology by quantitative EEG and psychometric methods.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):558, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, pharmacodynamic investigations in psychopharmacology by quantitative EEG and psychometric methods are described. It is maintained that by utilizing digital

computer period and power spectrum analysis of the EEG, it is possible to evaluate objectively and quantitatively the effect of psychotropic drugs on the human brain. Under double-blind condition, single oral doses are administered randomized and at weekly intervals to normal volunteers. The drug being studied is given in three doses and compared with placebo and a well known compound. EEGs are recorded before as well as 2, 4, 6 and 8 hours after drug administration. At the same time periods, psychometric tests are carried out including evaluation of attention, concentration, psychomotor activity, affect, mood, reaction time and flicker fusion. Based on the pharmaco-EEG profile, AX-A-411-BS was classified as anxiolytic drug. Its effect was found to be dose dependent, with the anxiolytic efficacy starting at 60mg, while at higher doses (90 and 120mg) additional sedative properties were observed. The time of onset of efficacy was as early as the second hour after administration, with the effect increasing up to the eighth hour. WA-335 (danitracene) was shown to be a CNS effective drug with an antidepressant profile. It induced dose dependent neurophysiological and psychological changes which started in the second hour postdrug and peaked between the second and fourth hours. Single oral doses of anorexigenic agents including 20mg fenfluramine and two different formulations of 15mg phentermine were investigated as well. In the latter study as well as in a study with a new retard form of oxazepam, blood levels were determined also. The relationship between blood level, psychometric, and quantitative EEG data is discussed. (Author abstract modified)

002727 Weingartner, Herbert. Adult Psychiatry Branch, National Institute of Mental Health, Bethesda, MD 20014 **Human state dependent learning.** In: Ho, B., Drug Discrimination and State Dependent Learning. New York, Academic Press, 1978. 392 p. (p. 361-382).

State-dependent learning (SDL) research in humans is discussed. The methods used in this line of research and their implications for demonstrating SDL are considered, and it is concluded that the presence of SDL effects is often determined as much by the methods used to test SDL as by the manipulations used to alter state. The results of studies using various drugs (alcohol, amphetamine, marijuana, physostigmine and barbiturates) to induce SDL effects are summarized. Studies of nonpharmacologically-induced SDL effects, including studies of state-dependent recall in patients with bipolar affective illness, are discussed. It is proposed that the findings have implications for theories of SDL as well as for the understanding of what constitutes a change in brain state with respect to a drug, neurochemical event or disturbed behavioral state. Theoretical models for SDL are discussed in relation to theories of information processing, memory, retrieval and memory dissociations. Possible applications for SDL, including study of cognitive development, are offered. 33 references.

002728 Westenberg, H. G. M.; De Zeeuw, R. A.; De Cuyper, H.; Van Praag, H. M.; Korf, J. Laboratory for Pharmaceutical and Analytical Chemistry, State Univ. Groningen, Groningen, The Netherlands **Bioanalysis and pharmacokinetics of clomipramine and desmethylclomipramine in man by means of liquid chromatography.** Postgraduate Medical Journal (Oxford). 53(Supp. 4):124-130, 1977.

A liquid chromatographic method developed for the determination of clomipramine and desmethylclomipramine in plasma is examined. The method is selective, rapid and sensitive, with detection limits of 2ng/ml for clomipramine and 5ng/ml for its desmethyl derivative. In routine analysis, 30 to 40 samples can be handled in one day. The method was applied to single dose studies with clomipramine in health volunteers. After oral administration, clomipramine appeared rapidly in the general circulation; the half-life of the drug was about 20 hours; metabolism to desmethylclomipramine could not be detected. It is reported that intramuscular administration resulted in sustained plateau levels in the blood for at least eight hours, followed by slow elimination which confirmed the relatively long half-life found in the oral studies. 14 references. (Author abstract modified)

002729 Zifferblatt, Steven M.; Wilbur, Curtis S. NIH, National Heart, Lung, and Blood Inst., 9000 Rockville Pk., Bldg. 31, Bethesda, MD 20014 **A psychological perspective for double-blind trials.** Clinical Pharmacology and Therapeutics. 23(1):1-10, 1978.

The psychological difficulties of long-term double-blind clinical trials are discussed, focusing on the psychological environment created for both subjects and staff in such trials. It is argued that the double-blind research design may create an unplanned source of bias for both participants and clinical staff, resulting in actions that may lead to blind breaking. This problem is attributed to the ambiguity required by double-blind studies; the subject cannot be expected to tolerate ambiguity about his health status for a long period of time, while the staff assigned to monitor protocol adherence further add to blind breaking because of ambiguity regarding their proper clinical role. Several steps are recommended to manage blind breaking within a trial, including improving the quality of medical care, more rigorous screening procedures, and maintaining a clinical environment that promotes accurate disclosure of blind breaking. 14 references. (Author abstract modified)

17 MISCELLANEOUS

002730 Armstrong, Barbara. Hospital & Community Psychiatry, 1700 18th St., N.W., Washington, DC 20009 **The use of psychotropic drugs in state hospitals: a legal or medical decision?** Hospital & Community Psychiatry. 29(2):118-121, 1978.

The effects of legal decisions regarding drug and therapy use in state mental hospitals, particularly in California, are explored, arguing that legal constraints have taken from physicians the authority to make treatment decisions, but have left them with all of the responsibility and medical liability. It is argued that bureaucratic requirements regarding the use of electroconvulsive therapy, and pending legislation regarding the use of psychotropic drugs, may compromise the quality of care afforded mental patients. It is suggested that such controlling legislation is partly the result of physicians not policing themselves as a psychiatric group, of patients who feel offended because of psychiatric failures or abuses, and because of current attitudes toward the practice of psychiatry.

002731 Axelrod, J. Section of Pharmacology, Laboratory of Clinical Science, NIMH, Bethesda, MD 20014 **Central catecholamine neurotransmitters and psychoactive drugs.** In: Van Praag, H., Neurotransmission and disturbed behavior. New York, Spectrum Publications, 1978. 312 p. (p. 6-18).

In a paper presented at a congress of the Interdisciplinary Society of Biological Psychiatry and the Dutch branch of the International League against Epilepsy held in Amsterdam, The Netherlands, in May 1976, the localization of catecholamine containing neurons in the brain and the biosynthesis, metabolism, storage, release, uptake, inactivation, and postsynaptic effects of catecholamines are briefly reviewed. The effects of various psychoactive drugs on each of these processes are discussed. It is suggested that psychoactive drugs, which act at the levels of formation, storage, release, and metabolism of catecholamine neurotransmitters as well as at postsynaptic receptors, have been useful in elucidating the physiological disposition and metabolism of these neurotransmitters and that this in turn has made it possible to elucidate the actions of psychoactive drugs. 37 references.

002732 Brodie, Jonathan D.; Rohrs, Charles C. Dept. of Psychiatry, New York University - Bellevue Med. Ctr., New York, NY **Margaret B. -- a "typical" Bellevue case.** Psychiatric Opinion. 15(1):35-39, 1978.

A case study of a typical Bellevue case is presented to demonstrate an approach to the problem of achieving adequate drug response, aftercare, and early tardive dyskinesia in the empirical manner characteristic of institutional psychiatry. Treatment variables considered are: 1) the nature of initial intervention; 2) precipitating circumstances leading to hospitalization; 3) choice of medication; 4) response to treatment; 5) availability of resources for continued hospitalization; and 6) the continuity of care in the medical model. Possible directions to improve approaches to patient care are also considered. 6 references.

002733 Bunney, William E., Jr.; Gulley, Blynn L. NIMH, Bethesda, MD 20014 **The current status of research in the catecholamine theories of affective disorders.** In: Usdin, E., Biochemistry of Mental Disorders: New Vistas. New York, Marcel Dekker, 1978. 268 p. (p. 83-100).

In a paper presented at the 1975 Intrascience symposium held in Santa Monica, California in December, 1975, research concerning the catecholamine (CA) hypotheses of affective disorders, which propose that depression is associated with a functional deficit of the CA neurotransmitters norepinephrine (NE) or dopamine (DA) at the neuronal synaptic cleft, is reviewed. The studies discussed involve: 1) investigations of the mode of action of drugs (alpha-methyl-p-tyrosine, reserpine, lithium, phenothiazines, butyrophenones, 3,4-dihydroxyphenylalanine, amphetamines, piribedil, and cocaine) which can activate or decrease manic or depressive symptoms; 2) investigations of pharmacological agents which affect specific aspects of DA and NE metabolism (synthesis, release, receptor sensitivity, uptake, and degradation); 3) measurement of DA and NE, their metabolites, and their synthetic and degradative enzymes, in body fluids and brain tissue of patients with affective disorder; and 4) neuroendocrine studies of pituitary hormonal factors (prolactin and growth hormone) thought to be under neuronal control of DA or NE and the effects of agents affecting DA and/or NE metabolism on these hormonal factors. It is suggested that cumulative data from these studies appear to be more compatible with a CA hypothesis of mania than with a CA hypothesis of depression. 79 references.

002734 Bylinsky, Gene. no address **/Psychoactive drugs and society./** A preview of the "choose your mood" society. Fortune. 95(3):220-227, 1977.

The spectre of a rapidly developing psychopharmacology technology being used by a society so that individuals are constantly taking drugs in order to alter their moods or potentials, is raised in the context of a discussion of various psychoactive drugs. The role of various amines in mental illness and normal brain functioning is outlined, and the similarity of some psychedelic drugs to these amines is discussed. Drug effects on creativity and sexual behavior are noted. It is contended that since no mechanism exists for the legal introduction and controlled use of most of these drugs, they will be illegally manufactured and sold on the black market.

002735 Campbell, Magda; Small, Arthur M. Department of Psychiatry, New York University School of Medicine, New York, NY **/Chemotherapy in mental disorders in childhood and adolescence./** Chemotherapy. In: Wolman, B., Handbook of treatment of mental disorders in childhood. Englewood Cliffs, NJ, Prentice-Hall, 1978. 490 p. (p. 9-27).

An overview of the current issues in pharmacotherapy with children and adolescents as a short-term treatment modality is presented. Discussions include: 1) drug efficacy methodology; 2) the decision-making process in implementing drug treatment; 3) choice of drug in various diagnostic categories; 4) drug administration issues including involving parents, dose regulation, polypharmacy and duration of treatment; and 5) an outline of the classification of drugs used most often with children and adolescents including the psychomotor stimulants, antidepressants, neuroleptics and miscellaneous antipsychotics, antiepileptics, antianxiety agents, anxiolytics and megavitamins. A tabular presentation of psychotropic drug classification and dosage is provided. 141 references.

002736 Carlsson, Arvid. Dept. of Pharmacology, University of Gotenborg, Fack, S-40033, Gotenborg, Sweden Anti-

psychotic drugs, neurotransmitters, and schizophrenia. American Journal of Psychiatry. 135(2):164-173, 1978.

A summary of the modes of action of antipsychotic agents and a review of the pharmacological profile of neuroleptics is presented. It is asserted that inhibition of central dopamine functions appears to be a common basic property of antipsychotic drugs. The mesolimbic and nigrostriatal portions of the dopaminergic system are probably the main targets for the mental and the extrapyramidal actions, respectively, of these drugs. The fact that dopaminergic hyperfunction induced by amphetamines or dopa may lead to a disturbance mimicking paranoid schizophrenia lends further support for a key role of dopamine in mental functions. Although a primary disturbance in dopamine function in schizophrenia cannot be ruled out, the intimate relationship between dopaminergic and other neuronal systems must be emphasized. The possible involvement of other amine, amino acid, or peptide transmitters in schizophrenia cannot be disregarded. 71 references. (Journal abstract modified)

002737 Carmody, John; Boyle, Richard; Butler, Patrick; Douglas, Philip; Dwyer, Dominic. School of Physiology and Pharmacology, University of New South Wales, Kensington, New South Wales 2033, Australia **Patterns of the use of benzodiazepines in Australia.** Medical Journal of Australia (Glebe). 2(20):666-668, 1977.

To examine benzodiazepine use patterns in Australia, complete records of the dispensing of benzodiazepines were collected over a 4 week period from 34 pharmacies in six suburban areas of Sydney, Australia, chosen to provide an economic cross-section of the city. Analysis of data indicated that these drugs constituted 3.7% of all dispensing. Of these prescriptions, 69% were for females: females outnumbered males in all three age groups examined by a ratio of more than two to one. Over 98% of all prescriptions were dispensed to individuals over 20 years old, and over 75% were dispensed to individuals over 40 years old. No socioeconomic correlations could be detected in the dispensing of benzodiazepines. Results are seen to disconfirm the popular stereotype of the female Valium taker. 4 references. (Author abstract modified)

002738 Creese, Ian; Burt, David R.; Snyder, Solomon H. Department of Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine, Baltimore, MD 21205 **Biochemical actions of neuroleptic drugs: focus on the dopamine receptor.** In: Iverson, L., Neuroleptics and Schizophrenia. New York, Plenum Press, 1978. 250 p. (p.37-89).

Studies of the dopamine (DA) receptor as a site of action of neuroleptic drugs are reviewed and discussed. Topics presented include: 1) the effects of neuroleptics on DA metabolism (synthesis, release, uptake, and turnover); 2) the actions of neuroleptics on DA sensitive adenylate cyclase; 3) evidence suggesting that the DA receptor may function physiologically in accordance with a two state model, i.e.,having both agonist and antagonist states; 4) methods of directly labeling the DA receptor, including evidence suggesting that tritiated (3H) DA labels the agonist receptor state and 3H-haloperidol labels the antagonist receptor state; 5) the mixed agonist/antagonist activity of lysergic acid diethylamide (LSD) at the DA receptor; 6) the direct labeling of the DA receptor by 3H-LSD in the caudate nucleus; 7) the correlation between the affinities of various phenothiazines and butyrophenones for 3H-haloperidol binding sites and their neuroleptic potencies; 8) the binding characteristics and sensitivity to various neuroleptics of DA receptors in different brain regions; 9) enhanced DA receptor binding after lesions of the nigrostriatal DA pathway to the corpus striatum and after some chronic drug regimens; 10) a radioreceptor assay for the measurement of blood neuroleptic levels; and 11) the usefulness of 3H-spiroperidol, which has a tenfold higher affinity for DA receptors and a lower affinity for alpha-noradrenergic receptors than does haloperidol, in labeling DA receptors in brain and pituitary. 107 references.

002739 Dews, P. B. Laboratory of Psychobiology, New England Primate Research Center, Harvard Medical School, Boston, MA **Origins and future of behavioral pharmacology.** Life Sciences (Oxford). 22(3-15):1115-1121, 1978.

The history of behavioral pharmacology is briefly outlined and the interchange between this discipline and psychology is discussed. Behavioral pharmacology, the study of drug effects in fairly intact individuals, got its real start with a 1937 paper by Skinner on the effects of caffeine and benzedrine on learning. The introduction of new drugs, such as the neuroleptics, and the creation of improved methods for studying behavioral effects in the 1950s resulted in increased growth in the field. Animal research into learning effects of amphetamine is briefly discussed to illustrate mutual interchange between psychology and behavioral pharmacology. It is suggested that most behavioral effects of drugs are understandable only as phenomena occurring in real time and in relation to other influences on the behavior. 15 references. (Author abstract modified)

002740 Duncan, Joan West. Clark University **Differential cue attentiveness and placebo responsivity. (Ph.D. dissertation).** Dissertation Abstracts International. Ann Arbor, MI, Univ. Mfilms, No. 77-20300 HC$15.00 MF$8.50 160 p.

The relationship of differential cue attentiveness and placebo responsiveness was studied to see whether Ss who rely on their own behavior in making self-attribution statements (self-produced cuers) respond differently from Ss who rely on contextual cues (situational cuers). It was assumed that the placebo response relies on manipulation of situational, not self-produced, cues, and that situational cuers would exhibit placebo response. Ss fearful of both snakes and electric shock were given placebos labeled as relaxers of arousers, then were exposed to fear stimuli and asked to rate their fearfulness. With shock fear, it was found that situational cuers showed less fear when given a purported relaxer, while self-produced cuers showed an opposite placebo effect (fear increased when they believed that the drug was having no effect on their condition). Self-produced cuers also differed significantly from situational cuers on a shock tolerance measure. Implications for self-attribution theory, drug evaluation research, and placebo administration are discussed. (Journal abstract modified)

002741 Edmiston, Susan. no address **/Concerning the use of Valium (diazepam)./** The medicine everybody loves. Family Health. 10(1):24-28,58, 1978.

The history and pharmacology of Valium (diazepam) are discussed in an interview with the drug's discoverer. Valium was found in 1957 as a result of a search by Hoffman-La Roche laboratories for a chemical with tranquilizing effects similar to those of meprobamate. It is noted that how the drug achieves its anxiolytic effect is not known, nor is it known exactly what constitutes human anxiety. The problems in the increase use and abuse of Valium are also addressed. (Journal abstract modified)

002742 Ermini, Marco. Institute of Pharmacology and Biochemistry of the Veterinary Medical School, Univ. of Zurich, Zurich, Switzerland **Is there a biological basis for geriatric pharmacotherapy?** Gerontology (Basel). 24(Supplement 1):1-5, 1978.

In a paper presented at a workshop on advances in experimental pharmacology of hydergine in Basel, December 1976, the problem of developing a geriatric pharmacotherapy is discussed. Combined scientific knowledge from biological, clinical and pharmacological research should be used as basis. However, in applied gerontology, direct relations to basic experimental gerontology are often avoided, because of its seemingly theoretical character. With some examples, it is pointed out that during the recent past, biological aging research has gained new knowledge, particularly on skeletal muscle and central nervous system aging, that can be used in the concept of a specific geriatric pharmacotherapy. 11 references. (Author abstract modified)

002743 Etevenon, P.; Pidoux, B.; Peron-Magnan, P.; Verdeaux, G.; Deniker, P. no address **BI and multivariate analysis of EEG data in clinical psychopharmacology.** Electroencephalography and Clinical Neurophysiology (Amsterdam). 43(4):478, 1977.

In a paper presented at the ninth international congress of electroencephalography and clinical neurophysiology in Amsterdam, September 1977, bivariate and multivariate analysis of EEG data in clinical psychopharmacology are described. Two groups of normal subjects have received an oral administration of anxiolytic compounds under different conditions. After habituation to the laboratory conditions, the first group, received a placebo administration at bedtime, 14 hours preceding the first control EEG recording, 24 hours later they received 5mg of nitrazepam followed the next morning by a second EEG recording. For each subject, spectral analysis of four posterior and anterior channels were computed for two successive sequences: 10 min in eyes closed situation and 5 min in eyes opened situation. In every subject, bivariate analysis reveals a decrease of alpha spectral intensity following nitrazepam. All subjects present this decrease of alpha activity and a major increase of 14 to 18 Hz activity which was statistically significant for P4-O2 but less significant for P3-O1. In a double-blind study, 10 other subjects received orally, a week apart, a placebo or two anxiolytic compounds. After the first control run, following oral administration, 10 min recordings were obtained every hour, over 7 hours. A general statistical strategy is proposed for quantifying psychotropic effects, in longitudinal as well as in transversal studies, based on statistical spectral analysis followed by applications of bivariate and/or multivariate analyses. (Author abstract modified)

002744 Extein, Irl; Goodwin, Frederick K.; Lewy, Alfred J.; Schoenfeld, Ronald I.; Fakhuri, Layla R. Clinical Psychobiology Branch, NIMH, 9000 Rockville Pike, Bldg. 10, 4S239, Bethesda, MD 20014 **Behavioral and biochemical effects of FK33-824, a parenterally and orally active enkephalin analogue (Unpublished paper).** Bethesda, MD, NIMH, 1977. 28 p.

Basic pharmacology of FK33-824, a pentapeptide, synthetic analogue of the naturally occurring methionine enkephalin (metenkephalin) is reviewed, and the effects of administration to normal volunteers in Europe and the U. S. are discussed. FK33-824 binds in vitro to opiate receptors and has many opiate-like properties. Evidence is accumulating that the endorphins play a role in a variety of CNS functions in animals and man. Laboratory and early clinical reports suggest that opiates and endorphins have effects on neuronal systems that regulate mood, thinking, and behavior. FK33-824 is a prototype of an endorphin-like drug which can be synthesized and administered to humans with relative ease and safety. Planned preliminary studies of FK33-824 in humans, both to characterize its clinical pharmacology and to assess its effects with schizophrenic and depressed patients are discussed. 26 references.

002745 Goldberg, Leon I. University of Chicago, Chicago, IL 60637 **Creativity in new drug development: an academic challenge.** Perspectives in Biology and Medicine. 21(2):188-195, 1978.

Increased academic participation in drug development is suggested to reverse the threatened demise of creativity in new drug development, on the premise that the high economic risk of totally innovative products has limited creative drug development within pharmaceutical firms. The costly and highly regulated procedures by which drugs are developed and tested for eventual use are described. It is hypothesized that perhaps only universities contain sufficient expertise to contribute both to the drug development process and to the evaluation of the impact of new drugs on society, while also maintaining a neutral position in controversial issues concerning government and industry. The formation of interdisciplinary academic research groups is suggested to investigate already synthesized chemical compounds, to capitalize on accidental clinical discoveries, and to investigate therapy for diseases of infrequent incidence. 8 references.

002746 Goodwin, Frederick K.; Potter, William Z. Clinical Psychobiology Branch, National Institute of Mental Health, Bethesda, MD 20014 **The biology of affective illness: amine neurotransmitters and drug response.** In: Cole, J., Depression: Biology, Psychodynamics, and Treatment. New York, Plenum Press, 1978. 250 p. (p. 41-73).

In a paper presented at a symposium on depression held in Belmont, Massachusetts in March, 1976, the role of amine neurotransmitters in affective illness and drug response is discussed. Knowledge of the functions of norepinephrine, dopamine, and serotonin (5-hydroxytryptamine, 5-HT) is discussed in relation to biological hypotheses of affective illness (amine hypotheses). Relationships between the therapeutic effects of drugs used to treat depression and mania and their biochemical effects are discussed. Difficulties in the interpretation of animal (laboratory) and human clinical data are emphasized. Studies of amine metabolites in the cerebrospinal fluid and/or urine of patients with affective disorder are reviewed. Methodological problems and difficulties in interpretation of data are discussed. Possible relationships between biological findings (amine metabolites and neuroendocrine correlates), pharmacological responses to antidepressants and lithium, and the identification of clinically distinct subgroups of patients with depression are discussed with emphasis on 5-HT function and metabolism. It is suggested that current biological and pharmacological data are consistent with, but not sufficient to prove, the existence of two biochemically distinct subgroups of depressed patients. 106 references.

002747 Gordon, Alistair M. St. Mary's Hospital, London, England **The biochemistry of depression.** Journal of International Medical Research (Northampton). 5(Supplement 4):81-84, 1977.

In a paper presented at a symposium on Ludiomil in general practice held at Torquay, England, in June 1977, theories relating to the biochemical causes and treatment of depression are

discussed. The hypothesis of the role of amines in depression is outlined. Postulating that depression involves a derangement of amine metabolism in which a deficit of amine activity occurs in certain areas of the brain which in turn results in altered transmission, the theory proposes that certain antidepressant drugs effect an elevation of brain amines restoring normal transmission and relieving the depression. (Author abstract)

002748 Gottschalk, Louis A. University of California Irvine Medical Center, 101 City Drive South, Orange, CA 92668 **Psychosomatic medicine today: an overview.** Psychosomatics. 19(2):89-93, 1978.

The current status of several areas of interest in psychosomatic medicine, including specificity theory, life changes, and peptic ulcers, is reviewed, and their relevance to the practice of psychosomatic medicine discussed. The importance of neuropsychopharmacological research to psychosomatic medicine is emphasized, and a perspective is given on the usefulness of drugs in conjunction with intensive psychotherapy. It is argued that the overuse of sedative hypnotic agents, such as the benzodiazepines, may block the capacity of the patient to remember or make use of some psychotherapeutic understanding. 33 references. (Author abstract modified)

002749 Gutheil, Thomas G. 74 Fenwood Road, Boston, MA 02115 **Drug therapy: alliance and compliance.** Psychosomatics. 19(4):219, 223-225, 1978.

The psychosocial aspects of prescribing psychotropic drugs are discussed as they embody and illuminate various aspects of the physician-patient relationship. Inclusion of prescribing phenomena within the framework of the therapeutic exploration, and maintenance of an alliance that permits participant prescribing, enhance the value of prescribing in the overall therapy program. Brief case studies are presented to illustrate transference, placebo effects, relationship equivalents of medication, food/gift symbolism of medication, countertransference, helplessness, and sexual dysfunction associated with psychotropics. 5 references. (Author abstract modified)

002750 Haber, Bernard; Aprison, M. H. Department of Neurology, University of Texas Medical Branch, Galveston, TX **Neuropharmacology and behavior.** New York, Plenum Press, 1978. 233 p.

A wide range of topics concerning central nervous system functioning are presented. Included are chapters on: 1) amphetamine psychosis as a model for paranoid schizophrenia; 2) a theory suggesting the presence of hypersensitive serotonergic synapses in clinical depression; 3) the organization of central catecholamine neuron systems (dopamine containing neuron systems, noradrenaline containing neuron systems, and adrenaline (epinephrine) containing neuron system); 4) the effects of reserpine on monoamine synthesis and on apparent dopaminergic receptor sensitivity in rat brain; 5) the induction of tyrosine-3-monooxygenase in rat adrenal medulla as a model for the transsynaptic regulation of gene expression; 6) the neurophysiological effects of diphenylhydantoin (phenytoin) and their relationship to anticonvulsant activity; 7) molecular aspects of neural mechanisms; and 8) an analysis of the seven major chemically oriented models of the neuron currently used in psychopharmacology. A complete bibliography of the works of Harold E. Himwich, a neuropsychopharmacologist in whose memory the volume was published, is included.

002751 Harford, Robert J.; Kleber, Herbert D. Drug Dependence Unit, 48 Howe Street, New Haven, CT 06511 **Comparative validity of random-interval and fixed-interval urinalysis schedules.** Archives of General Psychiatry. 35(3):356-359, 1978.

The comparative validity of random interval and fixed-interval urinalysis schedules in the detection of unprescribed drug use in drug dependents was discussed in a paper presented to the Third National Drug Abuse Conference held in 1976 in New York. These two methods of scheduling were assessed by comparing rates of detected opiate and quinine positive urine samples in a methadone treatment program for the period preceding (when a fixed-interval schedule has been used) and following implementation of a random interval schedule. Detected drug use doubled initially. As detection and clinical sanctions became more certain, drug use declined to well below its former level. Accurate detection of unprescribed drug use by addicts in treatment may facilitate their rehabilitation. Many clinics collect urine samples at random, using fixed-interval collection schedules, which are not free from sampling error. Random interval schedules minimize sampling error and consequently increase detectability of drug use by eliminating safe periods during which drug use cannot be detected. Programs that use fixed-interval schedules may underdetect drug use by more than 50%. If patients can reliably predict safe periods, the possibility of using drugs without fear of detection may impede their rehabilitation. 7 references. (Author abstract modified)

002752 Hebenstreit, G. Psychiatrische Abteilung, Landeskrankenhaus fur Psychologie und Neurologie, A-3362 Mauer bei Amstetten, Austria /**Psychopharmaceuticals in everyday practice.**/ Psychopharmaka in der Allgemeinpraxis. Wiener Medizinische Wochenschrift (Wien). 127(18):561-564, 1977.

The history and types of psychopharmaceuticals which have come into everyday use since 1952 are reviewed. Three groups are discussed: tranquilizers, which act on the limbic system as receptor blockers, thymoleptics, which produce the return of amines to the pool, and neuroleptics, which produce a release effect from the pool. Tranquilizers are sedative, while thymoleptics can be anxiolytic and depressant, positive mood inducing, or inhibition reducing, and neuroleptics bring about psychomotor and emotional dullness and indifference, with antipsychotic effects. Tranquilizers can be used effectively on a short-term basis for tension and anxiety reduction, but are habit forming and later cause withdrawal symptoms. On the other hand, thymoleptics can be used for months and even years in depression treatment while neuroleptics are more effective in clinical psychosis treatment. Effective therapy in all cases must take into consideration differences between inpatient and outpatient care as well as individual symptoms.

002753 Ho, Beng T.; Richards, Daniel W., III; Chute, Douglas L. University of Texas Health Science Center at Houston, Houston, TX **Drug discrimination and state dependent learning.** New York, Academic Press, 1978. 392 p. $23.00.

The study of drug discrimination behavior and state-dependent learning is examined. Specific topics discussed include: 1) the pharmacological actions and mechanisms by which various drugs, including levoamphetamine and other central stimulants, ethanol and other depressant drugs, nicotinic cholinergic receptor stimulants, muscarinis cholinergic receptor stimulants, cannabinoids, mescaline, narcotic analgesics and narcotic antagonists, pentazocine, and pentobarbital, may function as discriminative stimuli; 2) research strategies and techniques with emphasis on experimental design, data analysis, and statistical problems which may be encountered; 3) the

role of the state of the central nervous system in the acquisition of learned responses as well as memory disorders; 4) drug and nondrug manipulations which may alter the coding and availability of acquired information; 5) major theories of state-dependent learning; and 6) the implications of this line of research for understanding the processes of memory and learning.

002754 Huxley, Matthew. NIMH, 5600 Fishers Lane, Rockville, MD 20857 **Specs for a safe "high."** Chemtech. 7(9):530-535, 1977.

In response to the universal human desire to periodically alter the state of one's consciousness and to the current drug problem, criteria for the development of a socially acceptable consciousness altering drug are proposed. Techniques and mechanisms of altering consciousness are divided into means that alter the individual's external/situational environment, means that modify his psychic/ideational environment and means that alter man's somatic/pharmacological environment. Criteria proposed include: safety of the use of psychoactive compounds, societal safety factors, sanctions on purpose of use, sanctions on persons, sanctions on place, sanctions on provider, and various social problems.

002755 Joseph, Clifford; Chassan, Jacob B.; Koch, Maria-Luise. Hoffman-LaRoche Incorporated, Nutley, NJ 07110 **Levodopa in Parkinson disease: a long-term appraisal of mortality.** Annals of Neurology. 3(2):116-118, 1978.

To assess the effects of levodopa treatment on parkinsonism mortality rates, mortality rates for a group of 1625 patients in a collaborative multicenter study of levodopa (Larodopa) in the treatment of parkinsonism were compared with corresponding mortality rates in the general population adjusted for age and sex distribution in accordance with that of the parkinsonian patients under study. The death rate, conservatively adjusted for dropouts among parkinsonian patients, is estimated to be approximately 33% greater than that for the general population. This is in contrast to an earlier study of Hoehn and Yahr, prior to the advent of levodopa treatment, wherein the mortality rate for parkinsonian patients was shown to be in excess of that in the general population by a factor of 2.9, or nearly 200%. 7 references. (Author abstract modified)

002756 Lehmann, Heinz E. Douglas Hospital, 6875 LaSalle Blvd., Montreal, P.Q. H4H 1R3, Canada **Comprehensive clinical studies of psychotropic drugs.** Final Report, NIMH Grant MH-05202, 1977. 33 p.

The psychoactive characteristics and therapeutic efficacy of 34 new psychopharmacological compounds were investigated in both controlled and uncontrolled trials, and the effects of mega dosages of vitamins in schizophrenic patients examined. A total of 53 clinical drug trials were performed in either psychoneurotic or depressed patients, in psychogeriatric patients, and in schizophrenic patients. Nylidrine did not enhance the therapeutic efficacy of neuroleptic phenothiazines. The overall therapeutic efficacy of fluoxymesterone combined with thioridazine in hospitalized psychogeriatric patients was found to be superior to the efficacy of each drug when administered alone. Mega doses of various vitamins did not enhance the therapeutic efficacy of neuroleptic drugs and ECT in schizophrenic patients. Finally, there were no significant correlations between data obtained by psychometric test battery and the psychiatric diagnosis. 32 references.

002757 Ling, Walter; Klett, C. James; Gillis, Roderic D. Veterans Administration Hospital, Sepulveda, CA 91343 **A cooperative clinical study of methadyl acetate. I. Three-times-a-week regimen.** Archives of General Psychiatry. 35(3):345-353, 1978.

An open cooperative clinical study is presented in which the efficacy and safety of methadyl acetate (LAAM) was compared with methadone in the maintenance of 636 heroin addicts who had previously been stabilized on a maintenance regimen of methadone. The starting sample assembled by the 13 cooperating clinics were randomly assigned to continued maintenance on methadone (n=308) or crossed over to methadyl acetate (n=326) for a period of 40 weeks. The starting dose was identical to the previously established dose of methadone, but beginning with the second visit, dosage was flexible. Safety was evaluated by clinical and laboratory observations conducted at 4 week intervals throughout the study. Relative efficacy was evaluated by illicit drug use, program retention and attendance, and global staff judgments. It is concluded that methadyl acetate is as safe as methadone and, when given three times a week, is an acceptable and effective maintenance drug for many heroin addicts. 9 references. (Author abstract modified)

002758 Lloyd, A. H. Neuropsychiatric Research Group, CIBA-GEIGY (UK) Limited, Macclesfield, Cheshire, England **Practical considerations in the use of maprotiline (Ludiomil) in general practice.** Journal of International Medical Research (Northampton). 5(Supplement 4):122-138, 1977.

In a paper presented at a symposium on Ludiomil in general practice, held at Torquay, England, in June 1977, some practical considerations in the use of Ludiomil (maprotiline) in general practice are discussed. It is maintained that maprotiline is a tetracyclic drug with both sedative, tranquilizing and antidepressant effects which are all directly proportional to dosage. There are negligible effects on the cardiovascular system in man and it does not influence the central metabolism of 5-HT. All of these latter factors are in contrast to amitriptyline and imipramine. Maprotiline is a broad spectrum antidepressant and its use is indicated in the treatment of all types of depression. It is more rapid in its onset of action than tricyclic antidepressants, therapeutic response being produced in a few days, and it is slowly eliminated. It has been found to produce a minimum of side-effects, such as drowsiness and dry mouth. Its toxicity in accidental or suicidal overdosage is similar to that of the tricyclics, but is less in severity. Maprotiline has been shown to be rapidly effective in producing improvement in both agitated and retarded patients with various types of acute and masked depression. It is particularly effective as a substitute for monoamine oxidase inhibitors in the treatment of neurotic depression and in patients for whom electroconvulsive therapy would otherwise have been indicated. Other advantages of maprotiline are its weak anticholinergic action and its even weaker alpha-adrenergic blocking activity compared with amitriptyline. 93 references. (Author abstract modified)

002759 Lording, Douglas W. Medical Research Centre, Prince Henry's Hospital, St. Kilda Rd., Melbourne, Vic. 3004, Australia **Impotence: role of drug and hormonal treatment.** Current Therapeutics (Seaforth). 19(1):25,26,29-32, 1978.

The role of drug and hormonal treatment in management of erectile impotence is discussed. Background information includes discussion of the definition, prevalence, physiology, causes and clinical features of impotence. Methods of managing drug-induced, organic and psychogenic impotence are

described. It is noted that, in most men with impotence, no underlying organic factor can be identified and they are said to have psychogenic impotence. Use of psychotherapy and drug therapy in treatment is discussed. Specific drugs are recommended for use in treating different forms of impotence.

002760 Margetts, E. L. University of British Columbia, Vancouver, British Columbia, Canada /**Closing remarks at a symposium on obsessive-compulsive neuroses and phobic disorders.**/ Closing remarks. Journal of International Medical Research (Northampton). 5(Supplement 5):126-128, 1977.

In closing remarks presented at a scientific symposium on obsessive-compulsive neurosis and phobic disorders in Montreal, May 1977, the wide range of treatment modalities, etiologies, and research projects directed towards phobic disorders is discussed. Potential therapies include behavior therapies, clomipramine and other drugs, electrotherapy, psychosurgery, sleep therapy, and psychotherapy. The need for greater research into the zoological, chemical, and pharmacological causes of obsessive compulsive and phobic disorders is noted, and the importance of accuracy of terminology and reference is emphasized.

002761 Mason, Aaron S.; Nerviano, Vincent; DeBurger, Robert A. Eastern State Hospital, Lexington, KY 40508 **The results of a campaign to educate physicians in antipsychotic drug usage.** Hospital & Community Psychiatry. 29(2):100-101, 1978.

The methods and results of a campaign to increase the mental hospital physician's knowledge of psychotropic drugs and raise the hospital's standards of psychopharmacological practice in Kentucky is described. Lectures, seminars, distribution of reprint articles, review sessions in small groups or on an individual basis, and review of each physician's current medication orders were employed in the educational process. Basic principles emphasized the use of only one antipsychotic agent at a time, the use of antiparkinsonian drugs only when extrapyramidal side-effects appear and not in a prophylactic manner, the avoidance of polypharmacy, and the lowering of drug use as soon as the patient has been stabilized on a maintenance dosage. Statistics are cited which indicate that significant improvement in the physicians' prescribing practices for psychotropic drugs resulted from the peer review program.

002762 Mathews, Samuel James. School of Pharmacy, University of Connecticut, Storrs, CT 06268 **The use of lactulose in portal-systemic encephalopathy.** Connecticut Medicine. 42(2):96-97, 1978.

The use of lactulose in portal/systemic encephalopathy is discussed with attention to mechanism of action, efficacy, and adverse effects. Lactulose has induced overall improvement in up to 75% of patients, as is indicated by the reduction in asterixis, normalization of the electroencephalograph, and the lessening of mental confusion. Adverse effects are mild and tend to lessen with continued use. It is suggested that lactulose is interchangeable with neomycin in patients with chronic portal/systemic encephalopathy, and since it is less toxic than is neomycin, its use as maintenance therapy may be superior.

002763 Matthews, Gary. Dept. of Physiology, University of Colorado Medical School, Denver, CO 80262 **Strength-duration properties of single units driven by electrical stimulation of the lateral hypothalamus in rats.** Brain Research Bulletin. 3(2):171-174, 1978.

To examine subcortical neuronal responses to cathodal and anodal stimulation of the medial forebrain bundle and to assess their strength/duration functions, cathodal strength/duration functions were measured for 27 single units which were driven by electrical stimulation of the lateral hypothalamus. The distribution of chronaxies of these units showed four clusters at about 0.1, 0.25, 0.4and 0.5msec. These chronaxies are not fundamentally different from those previously reported for peripheral nerve. Two units fired repetitively during a long duration stimulated pulse. Anodal strength/duration properties were obtained from 14 units. Four units were not excited by anodal pulses of any strength or duration, four were excited during an anodal pulse (anode make excitation) but not at the termination of the pulse (anode break excitation), and six showed both anode make and anode break excitation. The data are discussed with reference to behaviorally determined strength/duration functions for brain stimulation reward. 7 references. (Author abstract modified)

002764 Matthysse, S. Dept. of Psychiatric Research, Massachusetts General Hospital, Boston, MA **Central catecholamine metabolism in psychosis.** In: Van Praag, H., Neurotransmission and disturbed behavior. New York, Spectrum Publications, 1978. 312 p. (p. 60-72).

In a paper presented at a congress of the Interdisciplinary Society of Biological Psychiatry and the Dutch branch of the International League against Epilepsy held in Amsterdam, The Netherlands, in May 1976, the dopamine (DA) theory of schizophrenia is discussed in terms of the following considerations: 1) is DA blockade related to the antischizophrenic actions of neuroleptic drugs or only to their side-effects; 2) is DA blockade a nonspecific effect of phenothiazine drugs, including those without antischizophrenic effects; 3) is there direct evidence for dopaminergic hyperactivity in schizophrenia; and 4) can the psychological actions of antischizophrenic drugs be explained in terms of DA blockade. Studies of the effects of thioridazine and clozapine in eight dopaminergic test systems in various animals are reviewed. These studies reveal that the two drugs have differential effects in several of the test systems and that they are effective in some systems and not in others. It is suggested that antagonism of amphetamine suppression of mesolimbic DA neurons, inhibition of stereospecific binding of DA to striatal membranes, and inhibition of adenylcyclase activation are systems in which antischizophrenic drugs with weak extrapyramidal properties have DA blocking effects in proportion to their psychological, rather than their motor, actions. Other animal studies are reviewed which indicate that the central dopaminergic test systems can differentiate between antischizophrenic phenothiazines and their clinically ineffective analogs. Studies in schizophrenic patients of cerebrospinal fluid levels of homovanillic acid, prolactin levels, brain dopamine-beta-hydroxylase activity, and dopamine stimulated adenylcyclase are reviewed, and it is concluded that there is no direct evidence for central dopaminergic hyperactivity in schizophrenia. It is proposed that the involuntary control of attention is at least partially under the control of a dopaminergic system. Studies of the effects of DA agonists and antagonists are discussed which suggest that the effects of antischizophrenic drugs may be explained by their effects on disordered attention. 55 references.

002765 McGlothlin, William. UCLA, Los Angeles, CA 90032 **Epidemiology of marihuana use.** In: Petersen, R. C., Marihuana Research Findings: 1976. Rockville, MD, NIDA, Research Monograph No. 14, 1977. 251 p. (p. 38-54).

Three surveys sponsored by the National Commission on Marihuana and Drug Abuse on present patterns and changes in

use of marihuana by American adults, youth, and students are discussed. The overall survey results show that marihuana has not been used significantly by the portion of adult population over 30 years of age, while use among youth, especially students, has increased at the national level. The recent American patterns of use seem to be based more on the adoption of a fad or lifestyle than on an attraction to the pharmacological properties of the drug. However, once introduced as a fad, it is quite possible that marihuana use will be sustained because of its pharmacological effects. Studies on the social and psychological correlates comparing personality and behavioral traits of students using and not using marihuana are discussed. Factors, such as childrearing practices, parents' drug using behavior, and peer influences which relate to the transition from nonuse to use of marihuana are examined. It is concluded that marihuana usage is frequently part of a larger pattern of nonconformity, but where longitudinal data have permitted adequate multivariate analyses, the results have generally suggested the lack of any causal effects. 49 references.

002766 Murphy, Dennis L. Clinical Neuropharmacology Branch, NIMH, NIH Clinical Center 10-3S229, Bethesda, MD 20014 **Animal models for mania.** In: Hanin, I., Animal models in psychiatry and neurology. Elmsford, N.Y., Pergamon Press, 1977. 499 p. (p. 211-222).

In a paper presented at a workshop on animal models in psychiatry and neurology held in Rockville, Maryland, in June 1977, animal models for mania are evaluated in the light of parallel studies in humans. The animal models reviewed include those based on the production of hyperactivity by: 1) low dose amphetamine administration to rats and mice; 2) morphine administration to mice; and 3) combined tricyclic antidepressant plus monoamine releasing drug administration to rats. The best evidence supporting the relevance of these models to clinical mania is their reversal by lithium pretreatment. These models are discussed in terms of studies in humans of interactions between lithium and: 1) amphetamine; 2) morphine; 3) monoamine oxidase (MAO) inhibitors; 4) desmethylimipramine plus tetrabenazine or RO4-1284; 5) L-DOPA; and 6) ethanol. The human studies indicate that lithium attenuates amphetamine-induced activation, euphoria, and hypomanic symptomatology and may block L-DOPA-induced hypsomania but does not affect euphoria produced by morphine or alcohol. Animal studies of the effects of lithium on nondrug-induced behaviors suggest that the drug has preferential effects on exploratory behavior or behavior in novel settings. In humans, lithium appears to diminish interest in novel stimuli and physical task initiation. The clinical features, etiology, biochemical factors (abnormalities in brain dopamine, norepinephrine, and/or serotonin) which may contribute to the production of mania in humans, and drug treatment of mania are briefly reviewed. A genetic model for vulnerability to mania in man based on platelet MAO activity is discussed in relation to behaviors in the rhesus monkey which have significant correlations with platelet MAO activities. 91 references.

002767 Naples, Maria; Hackett, Thomas P. Dept. of Psychiatry, Massachusetts General Hospital, Boston, MA 02114 **The amytal interview: history and current uses.** Psychosomatics. 19(2):98-99, 103-105, 1978.

The history and current uses of the Amytal interview is reviewed. Amytal is a moderately long-acting barbiturate with a moderately rapid induction time and is the drug most associated with the technique of narcotherapy. During the 1930s Amytal was used for the treatment of neuropsychiatric disorders and narcoanalysis. During World War II the drug was used to treat acute war neurosis. Presently Amytal is used in acute panic states following traumatic episodes, in cases of blocked psychotherapeutic exploration, acute hysterical amnesia, anxiety hysteria, conversion hysteria, and for differentiation of catatonic stupor from a stuporous depressive state. Medical and psychiatric contraindications for its use are outlined, and the proper interview procedure using Amytal is described. 31 references.

002768 National Research Council Committee on Clinical Evaluation of Narcotic Antagonists. no address **Clinical evaluation of naltrexone treatment of opiate-dependent individuals: report of the National Research Council Committee on Clinical Evaluation of Narcotic Antagonists.** Archives of General Psychiatry. 35(3):335-340, 1978.

To assess the clinical efficacy of narcotic antagonist therapy for opiate dependent individuals, a multiclinic controlled trial of naltrexone was undertaken with 192 postaddicts, methadone users, and street addicts. Analysis of data indicates that: 1) a narcotic antagonist is an acceptable treatment for a small number of patients undergoing treatment for opiate dependence; 2) the group most likely to be candidates for such treatment are those who are relatively opiate free (postaddicts) and well motivated to seek treatment; 3) although differences between patients treated with placebo and naltrexone were slight, both retention in treatment and opiate free urine tests favored the naltrexone group; and 4) adverse effects of relatively short-term treatment were slight, largely being symptoms and signs of precipitated abstinence in patients with residual dependence. 6 references. (Author abstract modified)

002769 no author. no address **International guidelines for clinical trials of psychotropic drugs.** Psychopharmacology Bulletin. 14(1):47-65, 1978.

International guidelines for clinical trials of psychotropic drugs as formulated by investigators from seven European countries, Brazil, Canada, Japan, and the U. S. are presented. Providing a common reference for planning, monitoring, analyzing, and interpreting clinical studies of the efficacy of investigational drugs in the treatment of anxiety, depression, mania, or schizophrenia, the statements describe sound current practice in the clinical investigation of psychotropic drugs. A sequence of drug trials is outlined, and provisions for monitoring and data collection and other methodological issues are discussed.

002770 no author. World Health Organization, Geneva, Switzerland **WHO expert committee on drug dependence: twenty-first report.** Geneva, World Health Organization, 1978.

Recommendations from the World Health Organization (WHO) to the United National Commission on Narcotic Drugs regarding substances to be controlled under the Convention on Psychotropic Substances, 1971, are presented. The Convention required that the therapeutic value of psychotropic substances be balanced against the risk to public health and social well-being arising from their use. The WHO Committee was directed to review all possible methods of classifying psychotropic substances under the Convention. It is pointed out that the Convention is intended to prevent and combat the abuse of certain psychotropic substances and the illicit traffic to which it gives rise through rigorous measures to restrict the use of these substances to legitimate purposes. Methods of evaluating substances were classified according to: 1) animal studies on psychotropic and dependence producing drugs; 2)

human pharmacology; 3) assessment of public health and social problems; and 4) assessment of therapeutic usefulness.

002771 no author. no address **Psychoactive drugs.** Journal of the Indiana State Medical Association. 71(1):8, 1978.

An American law which prohibits the return for trial of defendants under treatment with psychoactive drugs is criticized. This law is based on the question of whether the drugs which maintain mental competence produce side-effects that impair the defendant's ability to understand legal proceedings. It is asserted that psychotropic drugs are widely used by mentally competent individuals, do not impair intellectual functioning, and are less debilitating than other drugs, such as methadone, under which defendants may stand trial.

002772 Overton, Donald A. Temple University School of Medicine, Philadelphia, PA **Major theories of state dependent learning.** In: Ho, B., Drug Discrimination and State Dependent Learning. New York, Academic Press, 1978. 392 p. (p. 283-318).

Major theories or mechanisms that have been proposed for the production of drug-induced state-dependent learning (SDL) are described. Included are: 1) stimulus theories which propose that SDL is mediated by drug-induced production or modification of sensory stimuli; 2) the theory that SDL may be produced by drug-induced changes in affect or specific recall; 3) anatomical ablation theories, which propose that SDL occurs when some brain structures are made dysfunctional by drug; 4) other neurological functioning theories which do not involve anatomical ablation; 5) functional ablation theories which focus on the behavioral and cognitive consequences of drug action; and 6) theories resulting from investigations of verbal learning in humans which suggest that drug-induced changes in associative mediators or in visual scan movements produce SDL. Various nonpharmacologically produced types of SDL which may have important theoretical ramifications are discussed such as SDL produced by: 1) electroconvulsive shock; 2) brai lesions; 3) anxiety; 4) drive state; and 5) REM sleep deprivation. Theories relating SDL to drug abuse are also presented. Some postulated consequences of SDL in humans are discussed. A historical overview of reports of clinical dissociative phenomena in humans and of studies of drug-induced dissociation of memory is also presented. 222 references.

002773 Pagel, Melody L.; Sanders, Michael G. U.S. Army Aeromedical Research Laboratory, Fort Rucker, AL **Marijuana and human performance: an annotated bibliography (1970-1975).** Perceptual and Motor Skills. 45(3, Part 2):1125-1126, 1977.

A bibliography of 199 annotated references to aid the reader in determining the impact of marijuana on psychomotor, cognitive, and physiological factors considered pertinent to flight performance is advertised. The bibliography contains an index which categorizes the references into the following major areas: (1) reviews or overviews of issues, literature or research; (2) psychological effects of marijuana use; (3) physiological and pharmacological research; (4) medical comments and research critiques; and (5) additional reference sources. The basic period of coverage is 1970 to 1975, although selected studies from earlier years are also included. Primary sources utilized in compiling the bibliography are cited; however, the bibliography itself is not presented. 7 references. (Author abstract modified)

002774 Pedersen, Robert Smith; Jorgensen, Kaj Anker; Olesen, Anders Schou; Christensen, Kurt Norregaard. Dept. of Nephrology, Aalborg Hospital, South Section, DK-9100 Aalborg, Denmark **Charcoal haemoperfusion and antidepressant overdose.** Lancet (London). No.8066:719, 1978.

The cases of three patients treated with charcoal hemoperfusion for poisoning with tricyclic antidepressants are presented. Hemoperfusion started 3 to 4 hours after ingestion and stopped when artificial respiration was no longer needed. Hemoperfusion through a charcoal filter was evaluated as being highly effective in these three cases of accidental drug overdose.

002775 Pilette, Wilfrid L. Fitchburg-Leominster Unit, Worcester State Hospital, Worcester, MA 01604 **What is an adequate therapeutic trial of psychotropic medication?** Perspectives in Psychiatric Care. 15(4):170-174, 1977.

A case for more rational drug therapy than is beleived to be currently in practice is presented, and the need for more specific guidelines for adequate therapeutic trial is documented. It is contended that psychotropic medications are frequently prescribed in inadequate doses, in unwarranted combinations, are changed too frequently, and discontinued prematurely. Consensus on adequate dosage for psychotropic medications could probably be reached easily for both the antipsychotic and tricyclic drugs, since experts differ little in this regard. However, there is much disagreement as to the adequate time periods for therapeutic trials of antipsychotic medications. The possibility that time periods for antipsychotic drug trials should be different for acute and chronic patients is raised. 23 references.

002776 Rosin, Arnold J. Harzfeld Hospital for Chronic Diseases, Gedera, Israel **Treatment of dyskinetic and choreatic movement disorders in adults.** Gerontology (Basel). 24(1):46-57, 1978.

Results of a followup study on treatment of patients with buccal-lingual-masticulatory (BLM) type dyskinetic syndrome are reported. Involuntary movements due to chorea or facial dyskinesia were successfully treated in 13 out of 16 patients with antidopaminergic drugs of the phenothiazine, butyrophenone or reserpine type. In 3 of the 4 chorea patients, the movements were significantly suppressed, but with development of parkinsonian rigidity in 1 of them. 11 patients had buccal-lingual-masticatory movements, mainly from degenerative brain disease, and often associated with mild rigidity. Significant suppression of the dyskinesia occurred in 9 without unduly exacerbating the parkinsonism. The dose of drug could often be reduced over the following few months or years, and sometimes movements did not recur after withdrawal of the drug. It is suggested that treatment of choreatic syndromes could be carefully monitored, and that drugs should be reduced in dosage whenever possible. Combinations of dopamine-depleting and dopamine-receptor-blocking drugs may be effective, and the potential of central cholinergic activating drugs as useful treatment for dyskinetic disorders is also discussed. 27 references. (Author abstract modified)

002777 Sabin, James E. Harvard Community Health Plan, 690 Beacon St., Boston, MA 02215 **Research findings on chronic mental illness: a model for continuing care in the health maintenance organization.** Comprehensive Psychiatry. 19(1):83-95, 1978.

An analytical review of research findings relevant to continuing care of chronic mental illness within health maintenance organizations (HMO) is presented, and a treatment model of an HMO continuing care program is described. The use of psychopharmacological agents in the maintenance therapy of schizophrenics and patients with affective disorders is discussed. Patient compliance in taking long-term medications is addressed. The structuring of a therapeutic program, as it can be organized by an HMO, and the therapist's role in this program is described. The treatment model emphasizes the ongoing evaluation and assessment of the pharmacotherapy program for each individual patient. 72 references.

002778 Schwarz, Eitan D. Family and Mental Health Services of Southwest Cook County, Worth, IL **The use of a checklist in obtaining informed consent for treatment with medication.** Hospital & Community Psychiatry. 29(2):97, 100, 1978.

The makeup and use of an Informed Consent Checklist (ICC) which requires a minimum of time to review, fits conveniently into the clinical interview, can be used with all commonly prescribed psychoactive medications, fills only one page, and which can be inserted easily into the record as a permanent document signed and dated by the physician, is described. The ICC is administered initially near the end of the diagnostic interview before writing prescriptions, whenever medication is changed, and once a year thereafter. The checklist's sections cover the patient's medication and general medical history, drug side-effects, alternative treatments, benefits and precautions relating to a drug, patient response to the discussion, and physician recommendations. The ICC is suggested as a desirable alternative to the package insert since it keeps communication about medication within the doctor-patient relationship, enhances the relationship, and increases the patient's reliability and cooperation in his or her own treatment.

002779 Seeman, P.; Tedesco, J. L.; Lee, T.; Chau-Wong, M.; Muller, P.; Bowles, J.; Whitaker, P. M.; McManus, C.; Tittler, M.; Weinreich, P.; Friend, W. C. Dept. of Pharmacology, University of Toronto, Toronto M5S 1A8, Canada **Dopamine receptors in the central nervous system.** Federation Proceedings. 37(2):130-136, 1978.

In a paper presented at the 61st annual meeting of the Federation of American Societies for Experimental Biology, in Chicago, April 1977, research on dopamine receptors in the CNS is reviewed. Dopamine receptors in the central nervous system can be studied by measuring the specific binding of (3H)-dopamine, (3H)-haloperidol, d-(3H)-LSD, (3H)-dihydroergocryptine or (3H)-apomorphine. The receptors are stereoselectively blocked by (+)-butaclamol, a neuroleptic. All neuroleptics inhibit the specific binding of (3H)-haloperidol in relation to their clinical potencies. The radioligand that desorbs most slowly from the receptor is (3H)-apomorphine, thus making it a reliable ligand for dopamine receptors. Dopamine agonists that compete for (3H)-apomorphine binding do so at concentrations that correlate with their potency in stimulating striatal adenylate cyclase. Structure/activity analysis, using (3H)-apomorphine, confirms that the active dopamine mimetic conformation is the beta-rotamer of dopamine. Prolonged exposure in vitro of caudate homogenate to high concentrations of dopamine leads to increased binding of (3H)-apomorphine of (3H)-haloperidol, suggesting receptor sensitization. Chronic haloperidol treatment of rats leads to an increased number of dopamine/neuroleptic receptors in the striatum, but a decrease in the pituitary. 106 references. (Author abstract modified)

002780 Shochet, Bernard R. Institute of Psychiatry and Human Behavior, University of Maryland School of Medicine, Baltimore, MD **Use of mood-altering drugs in treating sexual problems.** Medical Aspects of Human Sexuality. 12(1):127-128, 1978.

The use of mood altering drugs in the treatment of sexual problems is reviewed with particular reference to the importance of the diagnosis and the etiology of the underlying dysfunction in the selection of treatment modalities. The physician's role requires elucidation of the nature of the disorder, treatment of the organic illness, and counseling of the individual patient and his or her partner. Neuroleptic agents, tricyclic compounds, lithium antianxiety agents, and other medications should be used as indicated by the psychological state of the individual patient.

002781 Usdin, Earl; Mandell, Arnold J. Pharmacology Section, Psychopharmacology Research Branch, NIMH, Rockville, MD **Biochemistry of mental disorders: new vistas.** New York, Marcel Dekker, 1978. 268 p. $26.55.

The proceedings of the 1975 Intrascience Symposium held in Santa Monica, California in December, 1975, are presented. Topics presented and discussed include: 1) differentiation between paranoid schizophrenia and hebephrenic schizophrenia based on clinical and genetic findings; 2) the use of electrophysiological indices as possible ways of understanding the structure and function of the organization of the brain and as tools in understanding mental health and mental illness; 3) studies utilizing lithium in rats to investigate the indoleamine hypothesis of affective disorders; 4) a review of studies of the catecholamine hypothesis of affective disorders; 5) studies of the effects of lysergic acid diethylamide and other hallucinogenic indoleamines on serotonergic neurons; 6) neurochemical and neuropharmacological studies of sleep disorders; 7) the effects of lithium carbonate on subjective state changes induced by sodium pentobarbital; 8) clinical and pharmacological studies of cerebrospinal fluid amine metabolites in patients with affective illness and schizophrenia; 9) the involvement of serotonin systems in psychotic states; 10) an integrative hypothesis based on research using lithium which may account for the various clinical types of affective disorders; 11) electron spin resonance studies of monoamine oxidase in brain and human platelets; and 12) heterogeneous functions of discrete serotonergic pathways in brain.

002782 Van Praag, H. M.; Bruinvels, J. Dept. of Biological Psychiatry, Psychiatric University Clinic, Groningen, Netherlands **Neurotransmission and disturbed behavior.** New York, Spectrum Publications, 1978. 312 p. $25.00.

The proceedings of a congress of the Interdisciplinary Society of Biological Psychiatry and the Dutch branch of the International League against Epilepsy held in Amsterdam, The Netherlands, in May 1976 are presented. The symposium addressed the transmission of impulses in central neurons as related to the regulation of behavior, with emphasis on the relationships between disturbances in neurotransmitter metabolism and/or functioning and the development of psychoses and affective disorders and on the effects of various psychoactive drugs on central neurotransmitter functioning. Specific topics discussed include: 1) catecholamine neurotransmitters and psychoactive drugs; 2) the influence of antidepressants on central monoaminergic systems; 3) central monoamine metabolism in depression and mania; 4) central catecholamine metabolism in psychosis; 5) the influence of neuroleptics on central dopaminergic systems; 6) the role of dopamine containing dendrites in the substantia nigra; 7) the interaction of

dopaminergic and other transmitter systems in the brain as related to the mechanism of action of neuroleptic drugs; 8) the measurement of enzymes related to monoamine metabolism as a diagnostic tool for neurological and psychiatric diseases; 9) the clinical significance of disturbances in the central gamma-aminobutyric acid system; 10) neuropeptides and behavior; 11) endocrine research in psychiatry; 12) the measurement of psychological functions as a method in human pharmacopsychology; 13) the use of direct, systematic observation in human psychopharmacology; and 14) the relationship between biological and environmental determinants of disturbed behavior.

002783 Weissman, Myrna M.; Prusoff, Brigitte A.; Klerman, Gerald L. Yale University School of Medicine, Dept. of Psychiatry, Depression Research Unit, 904 Howard Ave., Suite 2A, New Haven, CT 06519 **Application of life table method to naturalistic designs -- a comparison of efficacy of tricyclic antidepressants and benzodiazepines in ambulatory depressives.** Comprehensive Psychiatry. 19(1):27-36, 1978.

The utility of the life table method for analysis of longitudinal data collected under naturalistic designs is discussed, and its usefulness in approximating quasiexperimental conditions is illustrated in an analysis of relapse rates and of recovery rates in depressed outpatients who are receiving either tricyclic antidepressants or minor tranquilizers. The advantages and disadvantages of this life table method as compared with controlled clinical trials are discussed. It is pointed out that the life table method can resolve two particularly troublesome problems inherent in longitudinal studies: patient attrition and change over time. Further, it is inexpensive and does not interfere with clinical practices. The method can be used to compare any treatment as long as the outcome is defined and relevant data are available for classifying patients. It is concluded that although the method does not substitute for experimental controlled trials, it does provide a vehicle for obtaining results derived from large samples of subjects which can be extrapolated into generalized hypotheses of clinical and research significance. 16 references.

002784 Werry, John S. Department of Psychiatry, University of Auckland, Auckland, New Zealand **Pediatric psychopharmacology: the use of behavior modifying drugs in children.** New York, Brunner/Mazel, 1978. 416 p. $19.50.

The use of behavior modifying drugs in treating children aged 12 years and under is discussed. It is pointed out that the indications for the use of the drugs, as well as their pharmacologic effects, are very different from the indications and actions for their use in adults. Topics included in the first section include: 1) an introduction to clinical pharmacology (pharmacokinetics) including the absorption, distribution, metabolism and elimination of drugs and pediatric variations in pharmacokinetics; 2) methods of psychological and physical diagnosis; 3) drugs and cognitive processes and learning; 4) drugs and other psychological treatments; 5) social, legal and ethical issues pertinent to testing drugs in children and to treatment; 6) the principles of clinical trials; and 7) diagnostic classifications and indications for psychopharmacology. In the second section, individual drugs grouped therapeutically are examined. The types and chemical structures of the groups of drugs, pharmacology, clinical effects in children, side-effects, drug interactions, clinical indications, contraindications, usage and (where relevant) social and ethical issues are discussed. The groups of drugs examined include stimulants, antidepressants, antipsychotics, anticonvulsants, antimanic agents, antianxiety drugs, hallucinogens, sedatives and vitamins.

002785 Zito, Tom. no address /**Use of psychotropic drugs to alter psychic states.**/ Psychic presto: getting ready for the pick-your mood society. Washington Post. January 10: B-1, B-3, 1978.

Research and theories regarding the use of psychotropic drugs to unlock the human mind are discussed. Since it was discovered 2 years ago that the brain produces its own morphine-like substance that alters psychic states, the search has intensified for new drugs to change human moods and behavior. The effects being sought include enhanced learning states, reduced fear and anxiety, reduced need for sleep, safe intoxication, regulation of sexual response, manipulation of memory and guilt, and enhancement of esthetic appreciation. In individual experiments with psychotropic drugs, researchers have succeeded in eliminating the hearing of voices in schizophrenic patients; increase college students' abilities to write creatively; rejuvenate brain cells in the elderly; and restore sexual potency in impotent males. Concern is expressed for ethical consequences and long-term effects of provision of such drugs. If use of such drugs were to become common, it is concluded, psychiatry as we know it could become obsolete.

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[illegible] Zito, Tom. [illegible] (Use of psychotropic drugs in the [illegible].) [illegible] Washington [illegible] 1975.

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[illegible] Wong, [illegible] University of Auckland, [illegible] drugs in children. New York [illegible] 1976 [illegible]

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